VOLUME LXX

Hospital Library

NUMBER 6

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

June, 1942

Analysis of the Mental Defect in Chronic Korsakov's Psychosis by Means of the Conditioned Reflex Method. W. Horsley Gantt, M.D. and Wendell Muncie, M.D. 467

An Analysis of Deaths in the Operating Rooms of the Johns Hopkins Hospital with Special Reference to Those Occurring under General Anesthesia and Spinal Anesthesia. John Lyford, III, M.D., Olive L. Berger, R.N., and Harris B. Shumacker, Jr., M.D. 488

Difficulties in the Enzymic Titration of Duodenal Contents. Wilburt C. Davison 504

Book Reviews 517

Index to Volume LXX 519

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore, Maryland

Made in United States of America

Copyright, 1942, by The Johns Hopkins Press

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, MAXWELL M. WINTROBE

EDITORIAL BOARD

E. Cowles Andrus
Charles R. Austrian
James Bordley, III
Chalmers L. Gemmill
L. Emmett Holt, Jr.
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.85 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefor adjusted accordingly.

Subscriptions should be renewed promptly. To avoid a break in your series, subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

ANALYSIS OF THE MENTAL DEFECT IN CHRONIC KORSAKOV'S PSYCHOSIS BY MEANS OF THE CONDITIONED REFLEX METHOD[1]

W. HORSLEY GANTT, M.D. AND WENDELL MUNCIE, M.D.

From the Henry Phipps Psychiatric Clinic, The Johns Hopkins Hospital

Submitted for publication December 19, 1941

Korsakov's description (1) of a "special form of mental disturbance combined with multiple neuritis" called attention to a now familiar clinical syndrome in terms so clear that it remains today a paradigm of the organic defect states. "This mental disorder appears at times in form of sharply delineated irritable weakness of the mental sphere, at times in form of confusion with characteristic mistakes in orientation for place, time and situation, at times as an almost pure form of acute amnesia, where the recent memory is most severely involved, while the remote memory is fairly well preserved."

Aside from the types with stupor or confusion, Korsakov noted cases with serious disorder of memory in the presence of clear consciousness and intact judgment. "In these cases it is most striking, how the same patients who have good grasp of everything about them, and are able to hold an earnest conversation, have suffered so widespread memory loss that they literally forget everything immediately."

The clear cut character of the clinical syndrome has led to many attempts to define the basic disorder. Korsakov states: "The basic symptoms of the disease are usually the following: a marked degree of irritable weakness of the psychic sphere, then a more or less deep disturbance of thought association, and finally disorder of memory." From this it appears that Korsakov saw disorder both in memory and in formal thinking.

Later work has revolved about these issues. According to van der Horst's review (2), Bonhoeffer considered the thinking to be formally intact, the defect being one essentially of retention, the memory loss leading through embarrassment to confabulation. Kraepelin thought

[1] Read at the Neuropsychiatric Section of the Baltimore Medical Society, January, 1938.

the thinking was not completely intact, and with Fringo demonstrated experimentally with tachystoscopic images the retention defect. Pick (3) stressed the uncritical and senseless admixture of present and past experiences, leading to fantastic confabulations and allopsychic orientation. Grünthal (4) pointed out the disturbance in *Einstellung*, the directional orientation being influenced by the intrusion of experiences from the healthy phase of the patient's life, resulting in a short-circuiting whenever memory was demanded, and the appearance of disorientation and confabulation. Schilder and Hartmann (5) considered the memory defect to be more apparent than real, and related to disorder in the unconscious instincts and drives. They would speak of an inhibition of reproduction, rather than a real memory loss. Adolf Meyer (6) has always held that the Korsakov syndrome is characterized by relatively good use of material within the immediate range of the senses, but disorders whenever retention and memory were necessary for the performance.

Van der Horst elaborated Korsakov's remark concerning memory for time, and after painstaking analysis, saw in a loss of the sense for the flow of time the basic disturbance explanatory for all the important features of the psychosis—retroactive amnesia, fantastic confabulation, reduplicating paramnesia, disturbance in space orientation. He noted that judgment was defective only for items dependent upon the time factor. He drew attention to the good performance on school data and laboratory tests in contrast to the failure for memory of personal experiential data. He concluded that *dementia* in this psychosis means that "the immediate time conception and time as an order-principle are disturbed."

Werner Scheid (7) in a recent observation saw no thinking disorder, only a loss of orientation, retention and memory. Memory seemed to be unpunctuated by time, and qualitatively different from the normal, real experience and confabulations both being related as dream-like. Personal experiential memories were well handled, which he considered important for the understanding of the orientation. His patient found his way accurately over a previously familiar course, apparently with no memory of the whole or of the details, but by progression from one completed step to the next.

Gillespie (8), in a recent discussion of the component factors operat-

ing in amnesia, considers a retention defect, van der Horst's time factor, and the differentiation between *sensori-motor* and *personal* recall and memory as important for the understanding of the Korsakov psychosis. He refers to Meggendorfer's polyneuritic patient whose memory for personal data was better than for the impersonal—contrary to most clinical experience—to illustrate the difficulty in laying down a hard and fast rule.

In summary, then, a number of different kinds of defect have been noted as basic for the understanding of the Korsakov psychosis: retention and memory, formal thinking, the conception and appreciation of time as an essential psychological category, the personal experience determined versus the more mechanical sensory-motor memory. There has thus been no unanimity in explaining the defects; the analysis has usually not been carried beyond bare statements and descriptions. In an effort to relate the defects to each other and perhaps to a more basic disturbance our investigation was undertaken.

METHOD

Since the establishing of the laboratory for the study of psychopathology by the method of conditioned reflexes under the auspices of the Henry Phipps Psychiatric Clinic in 1929, attempts have been made to bring the Pavlovian method (9) into clinical use and to formulate its results in terms compatible with psychiatric orientation. Concerning the application of methods in the study of the Korsakov syndrome, Adolf Meyer says (personal notes):

"In contrast to the sufficiency of the simple stimulus-response tests of physiology, biology and especially psychobiology require obligatory consideration of the patterns of chains and sequences of reaction and interreactions. This holds especially when the use of memory stands in contrast to direct function. Hence the need of methods using well organized patterns and readily recorded time-sequences.

"The Korsakov complex first described in connection with polyneuritis presents an important experiment of nature allowing a study of the role and relation of memory in the newer and more important question of the nature and operation of retention and recall in the process of thinking and the determination of actual tissue damage in contrast to mere functional disorder. Hence the importance of adequate and readily usable methods controlling the time and choice factors. The studies of van der Horst and of Gillespie bring out this time factor and the personal

vs. mere sensory-motor factors in the memory disorder of the Korsakov type. They constitute tasks specific for the psychobiological organization.

"Familiarity with pattern technique becomes exceedingly helpful in recording the personal issue to readily controllable experiments recording both the order and complexity of the tasks which involve the symbolization and meaning and selective functions so strikingly affected in the confabulatory amnesia."

The Pavlovian method obviously deals with the emergence of meaning and symbolization in a special time-bound setting, the component items of which lend themselves to qualitative and quantitative analysis and measurement. Pavlov felt that his method had made psychology unnecessary, and prepared to speak in neurophysiological terms. The pragmatist will see, however, in some of the "explanations" of the phenomena a resort to speculation—of another sort to be sure than the one Pavlov was attempting to overthrow, but none the less baffling. It is not necessary to subscribe to the full Pavlovian doctrine to realize the advantages of the method. To our minds it appears an ingenious means of observation of the *learning* and *forgetting* process, and for this purpose we have used it clinically. *Learning*, initially a matter of choice for the patient, is made more nearly obligatory by being based on vital biological functions, food, defense against pain, etc.

Essentially the method consists in exposing the patient to a simple and orderly series of events chronologically arranged, and within the grasp of his sensorium. His spontaneous active participation and collaboration in this succession of events originally gained by the interest of the test situation, is clinched by appealing to his desire to avoid pain. In other words, this succession of events is not one to which he may remain casual and uninterested. The value of *sense* to him of the dénouement is the inspiration for the development of certain anticipatory defense reactions. In Pavlovian terms, these represent the conditioned reflexes. The Gestalt psychologist could speak of the setting up of certain field-forces by the sequence of stimuli which leads to a rounding out or closing of the gap by appropriate activity.

The patients were tested for their ability to react defensively in anticipation of an unpleasant stimulus: namely, to wink defensively to an anticipated tap at the base of the nose, or to withdraw the hand from an electrode plate in anticipation of a faradic shock. Similar results were obtained with both methods.

Several variations of the method with the hand withdrawal showed little difference in the results. The faradic shock unconditioned stimulus was applied either by having the patient place his right hand on two plate electrodes or wear a glove with the electrodes on the fingers. The shock was preceded by an initial (conditioned) stimulus (bell, light, buzzer, metronome) acting for 0.5 to 5 seconds. The defensive (conditional) response (abbreviated as CR) was noted by (1) any anticipatory movement of the muscles of the forearm and hand during the action of the initial stimulus; (2) if this failed to appear after a number of trials, the patient was asked to signal his anticipation of the shock by raising his hand from the electrodes, thus avoiding the shock; (3) or the patient was asked to anticipate the shock by closing a switch with the free hand and so short-circuit the current and avoid the shock. Simple observation of the changes in muscle tension is frequently inadequate as an estimate of a formation of the defense response (CR). Closing the switch or raising the right hand as a signal gives a more consistent and easily controlled observation.[2]

If the patient fails to react defensively, i.e., form a CR, by this procedure, he is asked to state what he thinks he should do; care is taken not to give him further directions. For example, the patient is told, "I want you to close the switch to avoid the shock and to close it before the shock comes. This you can learn to do by observing what goes on in front of you." If the patient fails after these directions, he is led by continued questioning to state what he is supposed to do. Frequently a better performance could be obtained, even though it lasted only a short while, through this verbal aid. If the patient still fails, his ability to carry out orders can be tested by telling him, "One of these signals, perhaps the red light, means that you will get shocked. When you see or hear the signal, I want you to close the switch." Under these cir-

[2] We leave out of consideration here the question of the complexity of the movement of throwing the switch compared with the simpler one of withdrawing the hand, realizing nevertheless that some distinction should be made between them. This distinction has been made by one of the authors by designating the spontaneous withdrawal of the hand or related muscular movements (equivalent to the dog's removing his foot from the source of the shock) as *primary* or spontaneous, and the throwing of the switch or other complex elaborated movements as *secondary* or integrated CR. At the present stage of our knowledge the nomenclature rests partly on an arbitrary basis inasmuch as we do not know the difference in the mechanisms involved in the two movements.

cumstances testing is in reality for the patient's span of retention after the statement and his capacity for executing previously formed defense responses (CRs) to command rather than any ability to react to a new situation.

The ability of the patient to differentiate between two signals, was also tested. After the patient had responded defensively (formed a positive CR) to one system of signals, e.g., to the red light plus shock, he was exposed to another series, e.g., a white light not followed by shock. The normal subject, after only a few trials, reacts at first as with the previous system, but then without being given further directions, stops reacting defensively to the series not terminating in a shock (8).

Apparently the success of the experiment depends upon (1) the degree of intactness of the sensorium, (2) the attention and concentration brought to bear on the task, (3) the ability to analyze the series of events for the ultimate meaning to the patient, and (4) the ability to synthesize the facts of analysis into a plan of action which will complete the "sense" of the experiment.

RESULTS

The following are typical protocols:

Case I. Summary: Korsakov's psychosis developing in a chronic alcoholic after the fourth bout of delirium tremens, alcoholic polyneuritis.

Patient W. G. B., male, butcher, aged 40 on admission to the Henry Phipps Psychiatric Clinic on October 22, 1929. Transferred to the Springfield State Hospital on March 20, 1930, where he has remained.

The patient, an obese pyknic man, of German descent, a chronic alcoholic (beer and whiskey), was first admitted to the Henry Phipps Psychiatric Clinic on March 19, 1928 in an acute alcoholic delirium with much manic-like activity. There was a history of alcoholic deliria, three and two months previously. He remained in hospital to May 31, 1928. Soon after leaving hospital he began to drink heavily, and lost his business because of his lack of interest and poor memory. In November, 1928, he began to experience difficulty in walking, developed some grandiose plans for making money through inventions. Strabismus and inability to walk unaided were present on admission. He was euphoric, his speech was disconnected, there was disorientation for time but not for place or situation, marked memory deficit, and visual hallucinations of beetles.

The delirious picture reduced gradually to one of residual defect. In the presence of good mood, he was disoriented for time and person. Recent memory for

experiential facts was poor, nor could he retain any of three objects after five minutes. On the contrary he retained nine digits forward, and school information was good. Evasions and confabulations, both of the *embarrassment* and the *fantastic* type, were present in abundance. Throughout his stay in state hospital he has remembered his former physician (W. M.) and a few facts concerning his stay at the Clinic. Physical examination showed polyneuritis involving the lower extremities and the external ocular muscles with strabismus, painful calves, and absent deep tendon reflexes of the lower extremities. The strabismus cleared in hospital but the tendon reflexes have remained absent. The liver was enlarged.

Experimental: This patient was first examined by the CR method described, on November 25, 1929, using a metronome of 100 beats (M 100) in anticipation of a shock to the hand and M160 to signal the absence of shock. After 50 trials there was no definite defense response; he never raised his hand with the signal. There was an ineffective and diffuse reaction to any signal, as shown by his verbal indication as to whether or not he had received the shock. Sometimes the patient would exclaim "Ow" when he received the shock and usually "Noch nicht" with the negative signal when he did not feel the shock. His remarks were the same with any signal, however. Frequently he would say "Noch nicht" with any signal during the period before the shock, showing some general vague anticipatory reaction without critical differentiation. The following day the patient failed in the test even after 35 trials. The speech reactions indicate that he had formed a generalized reaction to the whole experimental situation but there were no definite specific motor responses to the signals. Tests done on November 27th gave the same results. On December 6, 1929, after a nine day interval the patient had forgotten how to place his hands on the apparatus, although he had been able to remember previously on successive trial days. On December 18th an intensive training by the use of short intervals (5–10 seconds) between the shocks failed to facilitate the normal reaction formation. On December 19th two lights were used instead of the metronomes. After a period of intensive training-reinforcing—the red (R) light followed by a shock, the white light (W) without it—the patient on questioning was able to state that the current came with the red light but not with the white. He was able to state this correctly after an interval of one minute, but not after two minutes. He was able therefore to respond rather weakly to the visual stimuli, but the response was retained less

than two minutes. He did not react to the auditory stimuli M100 and M160.

On December 31, 1929, the process was repeated, using the eye wink as a defense to a tap at the base of the nose. He was able to react correctly after 3 or 4 trials when a short interval of about 20 seconds was used. Retention lasted for two to three minutes, but disappeared after four minutes. The patient did not differentiate between the signals for shock and the neutral signals.

On January 6, 1930, there was no retention of the response of the previous week. To tactile signals the patient reacted less readily than to visual.

The patient was next tested on October 15, 1936, after an interval of more than six years, during which time he had been in a state hospital. A new apparatus was used, operating, however, on the same principle as the other. The results were similar to those previously obtained. His memory for some distant events, family and former occupation, was good. The verbal reactions to the initial signals were of the same sort as they had been six years previously, although the words were different. After repeating the conditioned stimulus, a red light, 12 times at ten second intervals, no motor response was elicited. The problem, he stated, was to raise his hand when he felt the current, and when reminded that he was to raise it to avoid the current before the shock, he answered, "I won't know how to tell that." Some evidence of the effect of the patient's speech formulation was shown by the patient's beginning to lift his hand *after* the shock, though previously he had not lifted his hand at all. Again asked for his formulation, he replied, "I don't know, I can only make a poor guess."

Since it was seen that the patient retained old associations from the far past, in particular to word signals, an attempt was made to associate the conditioned signal of the series with the word "shock." When questioned, the patient was induced to admit verbally that the red light had been accompanied by the shock. Still he did not give the proper reaction to the red light until the direct command was given: "Lift your hand with the red light." The response to this verbal command was retained only during the next three trials, (the latent period gradually lengthened from 0.5 seconds to 1 second to 3 seconds), after which he lapsed back into raising his hand only *after* the shock.

At this point, by leading questions, the patient was again induced to formulate the problem correctly, in order to ascertain the effect of the patient's verbal formulation on the motor performance. When tested immediately the patient gave the correct motor response for the next six times with ten second intervals between stimuli. The latent period was short—only 0.5 second. Now the white light was introduced as a negative stimulus, i.e., without the shock, alternating with the positive stimulus, the red light, accompanied by shock. There was no differentiation, the patient reacting to W for the next sixteen trials as he did for R; the latent period was 0.5 seconds.

Paralleling his failure to differentiate as judged by the motor performance, when questioned, he showed no verbal appreciation of the difference between R and W. The difference between what happens with the red light and with the white light, he considered to be: "Space of time, nothing else, duration of light perhaps." When asked if he knew what happened after the red light and the white light, he replied, "No, doctor."

Instructed to notice carefully if there was a difference between R and W, he replied *immediately after* the first two conditioned stimuli (R and W), "With the red light there is a shock, with the white light none." For the next three trials he made the correct differentiation on the basis of his verbal formulation, removing his hand to R but not to W. With the beginning of the fourth trial the differentiation disappeared and the patient began reacting to W the same as to R. Ten second intervals were used; the differentiation, lasting for three trials, did not persist as long as one minute.

The effect of a command was again tried by telling the patient not to raise the hand with W. This he obeyed correctly for the next six trials.

A transfer to auditory stimuli was then made by telling the patient to consider the bell as equivalent to the white light and the buzzer to the red light. For the next nine trials his performance to the auditory stimuli was correct.

After a ten minute interval the patient had lost the differentiation to R and W, reacting to both in a positive way. However, after three trials the patient made a correct differentiation between R and W, and also between the two auditory stimuli after the third trial (no reaction

on first two trials) but his reactions were not as certain as they were before the ten minute interval. However, when the bell and buzzer were tried at this point, there was no clear-cut differentiation; the patient showed his uncertainty by asking for an explanation.

Thus, the patient when faced with the desirability of elaborating certain simple motor responses to certain sensory stimuli found himself unable to do so except after specific verbal instructions. Even then the differentiation made on this basis, to both auditory and visual signals, disappeared after ten minutes, but now they could be restored after only a few trials. This test suggests that the patient had a very restricted field of attention, and that his capacity for synthesis was impaired through his inability to consider more than one thing at a time.

There is evidence of the rapid disappearance of the newer learned responses, a picture of their fading: the disappearance of the negative conditioned responses but retention of the positive, with restoration of the negative (differentiation) after a few trials, but the complete disappearance of all of the conditioned responses to the less practised auditory conditioned signal.

The patient was able to repeat six digits forward, four backward; he always recognized and named one of us (W. M.), his former physician, and knew he had been at the Phipps Psychiatric Clinic but could not say when.

Case II. Summary: Korsakov's psychosis without polyneuritis. Etiological factors: Chronic alcoholism, lung tumor with possibility of metastasis. The possibility of a Korsakov's psychosis from local involvement of the basilar regions of the brain should be considered.

Patient S. L., male, race track clerk, aged 46 on admission to the Phipps Psychiatric Clinic on September 13, 1935. Discharged against advice to the care of his family on January 12, 1937. Died a few months later.

The onset remains rather indefinite since he was in contact with his family only infrequently. In the fall of 1934 his brother noted that he seemed confused and changed the trend of conversation without reason. On September 1, 1935, he suddenly suffered two convulsions, with an aura of pins and needles in his fingertips, and followed by incoherent talk, and a little later with spontaneous fantastic confabulations concerning his brother's activity. He was taken to hospital on September 4, 1935, with temperature of 100°, pulse 106. He was unable to differentiate odors, the optic discs were blurred, the right pupil was larger than the left, convergence was poor, there was right facial weakness, and impairment of percussion note over the left apex was noted. He was confused, disorientated for

time, drowsy, and showed incoherent and irrelevant speech; recent memory and retention were defective. Judgment seemed good, but insight was lacking. The provisional diagnosis was brain tumor. There followed two more convulsions, with twitching of the *right* side of the face, drooling, cyanosis, followed by thick speech. He was transferred to this Clinic on September 13, 1935. Examination here gave evidence of an expanding tumor of the upper lobe of the left lung with displacement of the trachea to the right and anteriorly. He was an obese pyknic man, but lost weight slowly in hospital. The voice was hoarse in the latter months of his stay. The cerebrospinal fluid showed from two to ten cells, Pandy positive, the mastic curves 3321000000, the Wassermann reaction was negative. The left palpebral fissure was slightly greater than the right. There was no evidence of aphasia, apraxia, agnosia.

He complained of the hoarseness and was apologetic about it, referring to it as the result of longstanding bronchial trouble; also he complained of his poor memory, which he said was only for things he had no interest in. He was in excellent rapport, was cooperative, enjoyed being subjected to tests. The mood was for the most part good, but there were blue spells of several weeks duration, which he attributed to being so long confined in hospital. He read a great deal, went for walks with friends, entered passively into the ward program. In the latter part of his stay he became somewhat careless in his habits, going unshaven, spending the day if allowed in pajamas and dressing gown, and spitting into the waste basket.

On admission he was disoriented for time and place, although he always recognized the place as a hospital even if he thought it to be in New Orleans. He recognized the physician as such, and soon learned and retained the name of one of us (W. M.). Somewhat later he was always orientated for place and person and fairly accurately for time, although this was variable and responsible for confabulation at times. For example, in December 1936, when asked the date he declared it to be October, and when then asked about the presidential election, declared it was still to be held, and that Landon and Roosevelt were the nominees. Management of material within range of the sensorium was excellent. He never remembered more than the barest outline of the ward program but on the contrary retained nine digits forward and his performance on memory for school data was good. Remote memory for personal experiential data seemed much better than recent. He confabulated easily at first when placed in a position of embarrassment because of his poor memory, and as already noted from defective time orientation ("Einstellungstörung" of Grünthal), but later in his stay confabulations were elicited with difficulty.

He suffered a number of convulsive seizures in hospital, with twitching of the left face, and weak thready pulse.

He gave a history of moderately heavy alcoholism (whiskey), but he was rarely drunk. One story not completely authenticated indicated that he had had no alcohol for six months prior to the acute onset in 1935. At no time did he show peripheral neuritic symptoms.

The patient had fifteen training periods between October 30, 1935, and November 7, 1936.

On the first day, October 30, 1935, the patient began to show a positive CR on the sixth trial of the light with the shock, latent period two seconds. There was no differentiation made with the second light when it was used continuously alone or when it was alternated with the first positive light.

November 18, 1935. The patient did not recall the previous test. After sixteen trials with the light-shock sequence no CR was formed. Then the patient was given instructions to raise the hand on anticipation of the shock. For the next seventeen trials the patient began raising his hand *after* getting the shock, but failed to do this on the succeeding twenty-two trials. Thus an adequate response was never formed, although the patient attempted to obey instructions by raising his hand after the shock. After an interval of ten minutes the patient failed even to raise his hand after the shock, except on the 78th and 80th trials, showing a lack of retention in carrying out commands in this period.

November 19, 1935. There was no retention of the events of the experiment of the previous day. After a test of 14 trials, the patient did not react to the conditioned stimulus. Then the problem was outlined to him; he did not remember the explanation from the previous day, but after the next two trials he gave an adequate response to the signal. When a tactile conditioned signal was introduced, he again responded adequately. He continued to react, however, after the shock was discontinued, even after twenty trials. He performed subtraction tests, e.g., 100 minus 7, correctly, showing relatively good retention of old verbal associations in contrast to the inability to form new responses to present stimuli.

November 20, 1935. Patient did not remember the details of what he did yesterday, but on seeing the apparatus he stated, "The light goes on and I get stung." The conditioned signal was given but the patient did not react. After the problem was explained he reacted adequately for the next twelve trials given at 20 second intervals. Retention was tested after an interval of ten minutes: the responses were then irregular, being present less than half the time. The patient's performance on this day showed clearly the aid derived from verbal formulation.

November 21, 1935. The patient was told on November 20 at the close of the experiment to try to remember what he did for the test the following day. When he entered the room he remembered having been there, thought he was here the day before. He showed uncertainty at the beginning of the experiment by asking, "Shall I raise my hand?" He did not remember details, "only that it stings." At the beginning of the experiment the patient raised his hand very slightly and uncertainly *after* the shock. Following four signal-shock sequences the retention for the procedure of the previous day was improved, as was shown by his spontaneous statement, "If I don't get a shock, I should leave my hand down; if I do I should raise it." At the thirteenth trial, the patient showed uncertainty, asking, "Am I supposed to raise my hand with the shock?" Insight was evident; he said: "I remember but have only slight recollection, I don't remember details, I remember I was here." His uncertainty was shown by the remark, "You want me to figure out the interval to avoid the shock?" (after the eighteenth trial). An explanation was given the patient at this point; on the twentieth trial after a correct performance he asked, "Is that what you mean?" On this day differentiation was made correctly for the first time. After a ten minute interval there was some retention of differentiation, but it was slight and uncertain. His uncertainty was also noted when he answered to the question, "You understand it now, don't you?", with "Yes, if I can remember it. Is that the idea, to remember it?"

November 26, 1935. At the beginning of the test the patient said he was supposed to touch the lights, later "to raise my hand when you apply the switch," showing, as previously, improved retention when placed in the situation. Having lost his differentiation, and *acting according to his own formulation* at the beginning of the test, the patient gave at first a positive response to both lights with the same latent period, 1.5 seconds. Later he made the differentiation on several occasions, but this differentiation was lost when a neutral tactile stimulus was introduced. The patient showed a retention of the positive conditioned responses for five days, a restoration of differentiation after only two trials, with its disappearance subsequent to the introduction of an extra stimulus.

December 9, 1935. Tested for verbal retention, the patient stated, "I had to touch the bulbs when they are lighted. If I remember cor-

rectly you asked me which one had lighted and I touched them as they lit." After the second trial the patient gave a positive response to both lights, showing no differentiation. After fourteen trials the patient stated: "I raise my hand to avoid the shock," showing some adaptation during the experiment. When asked, "Can you know when to expect the shock?", he answered: "No, I can't." There was thus a lack of consistency between the verbal formulation and the motor response, and a complete lack of differentiation after 45 trials.

December 10, 1935. Tested for retention of the experiment of the preceding day, the patient stated, "You asked me to raise my hand when I saw the light to evade the shock." (Is that all?) "That's all I remember now." Thus the patient showed a retention of all that he performed the day before, as he had made no differentiation either then in the motor performance nor verbally on December 10. After two trials the patient began to give a positive response to both lights without differentiation, and so continued for the next 70 repetitions. His formulation at this time was: "I'm to raise my hand to the light on the right side but to keep it still when the light on the other side lights." This was the reverse of the actual facts. When a tactile signal was introduced the patient reacted without differentiation as he did to the lights. Questioned about his ward life, he showed a lack of memory for special events, e.g., he did not know specifically what he did; in general he knew the routinely repeated acts. His memory was best for remote past important events such as the details of his family. After an interval of about ten minutes the patient gave a correct verbal formulation of the experiment.

In this experiment as well as in some others the patient elaborated responses better *to his own verbal formulation*, even though incorrect, than to the facts of the experiment. The patient's verbal statement overruled and could even upset a weak muscular response that had been elaborated during the experiment.

January 3, 1936. Remote impersonal memory was good, as usual, e.g., the 100−7 test was done accurately in 30 seconds. His memory for recent events was poor; he thought he was tested here a week ago but he did not remember the test. He showed no retention of his previous elaboration, and offered only irrelevant verbal responses. After three trials without instructions, when told to raise the hand on anticipating the shock, he gave for the next five trials a positive re-

sponse to the red light with a latent period of 4.5 seconds, and also made a correct differentiation between R and W. Moreover, the patient was able to adapt his performance to a reversal of the signals, i.e., now giving R as negative and W as a positive stimulus.

February 28, 1936. Tested for verbal retention he stated, "I remember the lights lit and I was to tell which one, whether the red, white or green." His motor retention was also poor; he did not react to R after four trials. On being given a formulation of the problem he reacted correctly to R and differentiated W (negative) after two trials. The differentiation between R and W was disturbed by introducing a combination of R+W (negative) just once; after this he reacted to both R and W as positive. This disturbance was similar to that caused in a previous experiment by introducing a tactile negative stimulus.

March 23, 1936. The 100−7 test was done without error in 26 seconds. On being told to follow the same procedure as he did the last time, he said, "I remember when a certain light is lighted I didn't get a shock and I was told something about raising my arm." For four trials with R *before* this statement by the patient he did not raise his hand, showing a lack of memory for the specific details. After his formulation he raised his hand to R, with a latent period of two seconds, showing the effect of his speech formulation upon his reaction. On stating after the next two trials of R, "I know I get the shock with R and not with the others," he differentiated between R and W also by the correct hand movement. The patient, however, was unable to adapt to an extinction experiment (where the positive stimulus is converted into a negative by failure to follow the signal with the shock).

October 5, 1936. The 100−7 test was done in 28 seconds. The patient said he remembered seeing the apparatus before: "Yes, the colors light up and you ask me which colors they are." His memory for recurring recent events of interest to him, such as going to the cinema every Saturday with a friend, was good, but he did not remember the specific separate events such as what he saw at the cinema. On the first ten trials of R (shock) the patient gave no overt response, and there was no visual evidence of any anticipatory muscular activity in the arm or body. After outlining the problem to him he reacted to R correctly twice out of six trials. At this juncture the patient when asked what he was supposed to do, said, "Raise my hand

before the light went out," which he did correctly for the next three times. He differentiated W from R on the first trial, but extinction was impossible for him.

October 28, 1936. The 100−7 test was done correctly in 55 seconds and the patient remembered going to the cinema with his friend but not what he saw. Asked about the apparatus he said: "I put my hand down and call those lights." Without further instructions he failed to respond adequately to R after five trials, but when reminded that he must raise his hand when he expected the shock he performed correctly and maintained it for the next five trials, also making a differentiation to W. The effect of verbalization was evident in this experiment.

November 7, 1936. The patient gave an incorrect verbal formulation of the problem, and no reaction to R or W. After being told to lift his hand when he anticipated the shock, he elaborated both positive and negative conditioned responses, i.e., reacted correctly to significant and neutral signals but failed with extinction.

Case III. Summary: Korsakov's psychosis in a chronic alcoholic, with polyneuritis.

Patient, H. S., male, railroad employee, was 53 years old on admission in February, 1927, to the Springfield State Hospital, where he has remained since.

The patient, a chronic alcoholic, developed in the fall of 1926 pains in and weakness of both legs. Soon appeared confusion, disorientation for time and place, spontaneous fantastic confabulations concerning his wealth and ownings. He had auditory and visual hallucinations (content not noted in the record), and delusions of his property being stolen. He was brought to hospital because of his restlessness, insomnia, and irritability.

In hospital except for occasional outbursts of irritability he has caused little trouble, appearing cheerful, cooperative, talkative, with little initiative and easily led. He confabulates freely both spontaneously and when embarrassed by his poor memory. He is disorientated for time, place, person. He states he is in Wheeling, West Virginia (his former home), and the physician is always "Frank," an Italian fellow laborer on the railroad. When the physician takes his fountain pen from his pocket, the patient volunteers that he invented the fountain pen.

The hospital records him as having auditory hallucinations of an indefinite character. The memory is very poor, especially the recent. Retention is poor. Serial subtraction is good as long as he can retain the task. General information, judgment and insight are very poor.

He is a tall pyknic man; the pupils are unequal and react sluggishly to light; deep tendon reflexes are sluggish or absent.

October 15, 1936. This patient was badly disoriented as to time, place, and person. As usual he remembered one of us as "Frank." The last president recalled was Theodore Roosevelt. The 100−7 test was done with only one error. When asked what season of the year it was, the patient looked out of the window, saw the green leaves, and said, "Spring." In these last two performances could be seen the persistence of old associations. This patient made the worst performance of any patient in the series. He could not recall after one minute the outline of the problem, nor the signal used. In order to give the best opportunity for response elaboration very short intervals were used between shocks (5 seconds), and verbal aid was secured by having the patient repeat the word, "shock," when the R came on. After repeating 35 times the verbal combination, "red light-shock," and when told to raise his hand instead of saying, "red light," he did this correctly for three times until W was introduced; thereafter the reaction disappeared. The patient returned to a stereotyped repetition, saying "Red light," to the signal. This patient under the most favorable circumstances of this situation showed only a generalized type of reaction without the slightest differentiation. His retention was extremely short. There was absolutely no insight into the problem.

ANALYSIS OF THE EXPERIMENTAL DATA

The series of patients presents a fairly uniform picture of inadequate performance in the test situation, and distinctly different performance from that of normal subjects. Keeping in mind the factors decisive for the test, this failure must be thought to be due to disturbance in one or more of the following: sensorium, attention and concentration, analysis of the situation, and synthesis of an appropriate activity.

Disturbance of the sensorium can be ruled out even when the patient showed disorientation to formal questioning, in view of the almost perfect accuracy in reporting the perception of the conditioned stimuli (visual, auditory), and of the terminal unconditioned stimulus (pain-shock). There was a tendency to a reduced threshold of perception of the painful stimulus.

Attention and cooperation defy quantitative, or even accurate qualitative, estimation. In general they varied from good to poor, with mood playing no significant role. The patients were pleasant,

for the most part apparently interested, but the interest was at times difficult or impossible to sustain. Frequently the patient would have to be recalled to the task from an apathetic inattentive attitude. This was true especially for patient H. S., who also gave the poorest performance, and who by clinical standards was also the most deteriorated. The verbal responses were spontaneous, profuse and usually relevant to the elements of the examination; for example, the patient would frequently announce each event of the test, as "red light, shock!" The patients showed no distractibility in response to chance environmental stimuli. It is our conclusion that the effect of disturbance of attention and concentration cannot be excluded, but that it probably is of minor importance in comparison with the effects of disturbance in analysis and synthesis.

The final activity of the patient is the product of his analysis of the situation and synthesis of an appropriate method of collaboration, but these two factors cannot always be clearly differentiated. Not one of these patients when warned only by the evidence of his own eyes, ears, and tactile organs (conditioned stimulus), was able to form an appropriate muscular defense to the initial stimulus. After verbally outlining the meaning of the problem, all but one were able to form weak adequate responses to visual signals, and all but two to both visual and auditory signals. The retention of these newly formed conditioned reflexes varied from 60 seconds to almost 10 minutes, but there was some retention of a more generalized reaction to the whole experimental situation for a longer period—in one patient for several weeks. After the formation of one conditioned reflex there was a tendency to generalization, so that the patient reacted similarly to all the visual stimuli. Of primary importance appears to be the failure in analysis of the time factor, shown in the patient's ability to report from memory the separate items of the test, but the universal despair at relating the events so as to achieve a satisfactory defense against the unpleasant finale of the test. It is also remarkable that the repetition of the test after the formation of an adequate response does not serve to establish it more firmly. In fact it fades with repetition and soon disappears. This must be attributed to poor retention.

After adequate positive response was obtained, complication of the task by the introduction of another signal to be differentiated proved

very difficult or impossible. Such negative conditioned responses when formed were unstable and of short duration; their span of retention was shorter than that of the positive conditioned responses. So much verbal help was necessary that it is questionable whether the patient was simply attempting to carry out instructions, or was really elaborating a new conditioned response, i.e., adapting to the situation spontaneously.

Experimental extinction of a positive CR (by repetition of the conditioned stimulus, not followed by the shock) was impossible, although spontaneous loss through lack of retention occurred. The patient's inability to react adequately was usually accompanied by an inadequate verbal formulation of the test. It was sometimes striking, however, to what degree the verbal formulation, which the patient could be induced to make, could determine the performance. This constituted an experimental proof of the importance of the "Einstellung." The subsequent performance was plainly seen to agree with the patient's verbal statement, showing a certain degree of retention for his own declaration, but the span of such congruous performance was limited. Not always, however, did the motor performance and the verbal formulation agree; the patient might react correctly and state the problem wrongly, or *vice versa*. Then the performance, motor or verbal, was a matter of pure chance, or there was thinking disorder, of a sort to admit paradox and incongruity without criticism.

In contrast to great difficulty in forming the conditioned reponse even with considerable verbal help, the patients were able to perform correctly, and apparently easily so, when simply told what to do—i.e., when the examiner made the analysis and synthesis for them. In such event correct performance was simply a matter of the utilization of old responses to verbal command, and its effectiveness depended upon the retention span which was adequate for successive tests. The insertion of a resting period of ten minutes, however, destroyed this simple response.

To be contrasted with the difficulty in forming new responses in the experimental situation, is the preservation of old responses and verbal associations. It is these which give to the Korsakov patients the semblance of plausibility; for example, most of these patients could perform the subtraction test correctly and rapidly; much of the ap-

parently "sensible" conversation of the patients was only the rehearsing of old muscular responses, or reciting old verbal associations.

The patients did not show obvious confabulation in the test situation. It is possible that some of the vague formulations presented were in the nature of "embarrassment" confabulation, or the result of a tendency to round out an experience with inadequate data from the poor retention.

SUMMARY AND CONCLUSIONS

The tests give experimental proof for: (1) Retention deficit, the span being sometimes very short; (2) poor memory for learned material, except in the most general, vague and impractical manner; (3) special difficulty in recognition of values of separate items of the test, when each item could be named; since this value in large part depends upon the chronological placement of the items, van der Horst's time factor is corroborated; (4) the importance of the verbal formulation for the determination of the "Einstellung"; (5) the complete inability to analyze and synthesize when left to the spontaneous use of the sensorium, unaided by verbalization; (6) motor and verbal formulation inconsistent one with another, indicating probable thinking disorder, in the failure to exclude paradox; (7) the failure for new learned responses ever to become "fixed" by repetitions, no matter how numerous, probably because of retention defect, in contrast to the preservation of old responses; (8) the ability to carry out direct command, again with the limitation of the retention span.

From these facts, the conclusion may be made that (1) retention and memory are badly disturbed in the presence of essentially intact sensorium; that (2) a clear distinction must be drawn between the completely spontaneous and the verbally aided formulation and performance, to the clear advantage of the latter; that (3) the sense for time and values is grossly disturbed; that (4) the "Einstellung" reflects the verbal formulation; that (5) formal thinking disorder exists; and that (6) new experiential data present a greater difficulty than more impersonal data, either new or old. The role of the tendency to "round out" experience in the production of random activity, and specifically in confabulation, needs further research. This tendency may be related to the euphoric mood and to the patient's previous personality.

Ability to form conditioned responses and their retention were roughly parallel to the clinical condition of the patient. An analysis of our material shows why the Korsakov patient is helpless in a situation involving any new elements. Changing signals, cues, to which the normal must ever adapt, have no meaning on the basis of present experience to the Korsakov patient; even when he is able under rigorous training to learn to react to a signal, he can not usually differentiate it from other physically similar but meaningless signals, and the retention of any recently acquired response is too short to be of practical value. The Korsakov patient thus lives *on* the past perhaps rather than *in* the past, on a meager fund of what has been salvaged from his more or less remote experiences, while the present with its demands for new responses is entirely beyond his horizon.

BIBLIOGRAPHY

1. KORSAKOV, S. S.: Über eine besondere Form psychischerstörung, combiniert mit multiplen neuritis. *Arch. Psychiatrie*, **21:** 669, 1890.
2. VAN DER HORST, L.: Über die Psychologie des Korsakows syndroms. *Monatschr. f. P. u. N.*, **83:** 65, 1932.
3. PICK, A.: Beitrag zur Pathologie der Denkverlaufes beim Korsakow. *Zeitschr. Neur.*, **28:** 344, 1915.
4. GRÜNTHAL, E.: Zur Kenntnis der Psychopathologie des Korsakowschen Symptomenkomplexes. *Monatschr. P. u. N.*, **53:** 89, 1923.
5. SCHILDER, P., AND HARTMANN, H.: Zur Psychologie Schadelverletzter. *Arch. Psych.*, **75:** 287, 1925.
6. MEYER, ADOLF: Lectures and Notes from the Phipps Psychiatric Clinic.
7. SCHEID, W.: Zur Pathopsychologie des Korsakow's Syndroms. *Zeitschr. Neur.*, **151:** 346, 1934.
8. GILLESPIE, R. D.: Amnesia. *Arch. Neur. and Psych.*, **37:** 748, 1937.
9. GANTT, W. H.: The details of the test method are to be found in:
   1) Cortical Function and Skin Sensitivity. *Arch. Neur. and Psychiat.*, **40:** 79–85, 1938.
   2) Impairment of the Function of Adaptability as Measured by a Simple Conditioned Reflex Test in Certain Psychogenic Contrasted with Organic Diseases. *So. Med. Jour.*, Nov., 1939.

AN ANALYSIS OF DEATHS IN THE OPERATING ROOMS OF THE JOHNS HOPKINS HOSPITAL WITH SPECIAL REFERENCE TO THOSE OCCURRING UNDER GENERAL ANESTHESIA AND SPINAL ANESTHESIA

JOHN LYFORD, III, M.D., OLIVE L. BERGER, R.N., AND HARRIS B. SHUMACKER, JR., M.D.

From the Department of Surgery, the Johns Hopkins Hospital

Submitted for publication April 6, 1942

Although anesthesia has been one of the valuable adjuncts by means of which surgery has been advanced to the present satisfactory state, it is apparent that it is still attended by inadequacies and hazards. Accurate data concerning anesthetic deaths are difficult to obtain because these are not often reported. The purpose of the present study was to analyze the deaths which occurred under general anesthesia and spinal anesthesia in the general operating rooms of the Johns Hopkins Hospital between July 1, 1931 and July 1, 1941. It was our chief concern to determine the frequency of such deaths, the proportions of these that seemed to be related to the anesthesia, and the percentage of those related to the anesthesia that might possibly have been avoided. We were also interested in learning whether there was any common cause for the majority of these possibly avoidable deaths. In such a study one cannot give conclusive data concerning the relative safety and efficacy of the various anesthetic agents, or concerning the important questions of the suitability of the anesthetic agent or its effect upon the ease or difficulty of postoperative convalescence. However, we have attempted to follow a plan which would allow as useful an analysis of the problem as possible.

The authors reviewed the records of patients to whom 51,392 anesthetics, general and spinal, had been administered in the general operating rooms of the hospital for all types of surgical procedures, except obstetric and opthalmologic, during the ten-year period from July 1, 1931 to July 1, 1941. The anesthetic agents were administered by a number of different anesthetists, and the operations were performed by a number of different surgeons. Records of the anesthetics which were administered in the emergency out-patient clinic have not

been included because these data were too incomplete to be analyzed satisfactorily. Operations performed under local anesthesias were the subject of a previous communication (1). Only those fatalities which occurred in the operating rooms were included in the present study, and none have been included in which the patient died at any time after having left the operating rooms.

A total of 75 deaths occurred in the operating rooms during the administration of the 51,392 anesthetics. As well as could be determined from a careful study of the records and from consultation when possible with the operator, assistant, or anesthetist, 55 (73.3 per cent) of the 75 deaths were unrelated to the anesthesia, and 20 (26.7 per cent) seemed to be related to the anesthesia (Table I). In some instances it was admittedly difficult to be certain of the cause of death. We

TABLE I

Distribution of operating room fatalities

		DEATHS		PER CENT
Total deaths under anesthesia in the operating rooms		75		
Deaths related to the anesthesia		20		26.7
Deaths not related to the anesthesia	Intracranial operations	29	55	73.3
	Transthoracic operations	16		
	Miscellaneous operations	10		

have classified as deaths related to the anesthesia all those in which the question of an anesthetic death was raised by the operator or the anesthetist, except a few in which another obvious cause of death existed.

ANALYSIS OF THE DEATHS UNRELATED TO THE ANESTHESIA

Twenty-nine of the 55 deaths thought to be unrelated to the anesthesia occurred during difficult craniotomies. Some of these patients died from hemorrhage, and all were in critical condition from increased intracranial pressure at the time of operation. These deaths included cases of hydrocephalus, tumors of the anterior or posterior fossa, and traumatic cases in which the intracranial pressure had been increasing steadily during the preliminary period of conservative treatment. Sixteen deaths occurred during difficult chest operations, many of the

patients being critically ill at the time of operation. Of these 16 deaths 9 occurred during pneumonectomy or lobectomy; one during pulmonary plexectomy in a critically ill patient with asthma; one during an attempted repair of an esophagotracheal fistula in an infant three days old; one during resection of a carcinoma of the esophagus; one during resection of the lower esophagus and cardia for carcinoma; and 3 resulted from obstruction of the respiratory tract by material from tuberculous or pyogenic cavities which emptied during the operation. Six additional deaths seemed to be attributable to the poor condition of the patients at the time of operation: one was in shock from trauma; one was critically ill with pancreatitis, another with peritonitis, another with severe hyperthyroidism, a proper subsidence of which could not be achieved by the usual methods; one had uremia; and one was an infant two days old who had a large adenoma of the thyroid. Two other patients died obviously from operative hemorrhage and shock, one during a nephrectomy and one during the resection of a Wilms' tumor. The case history of one patient was not available for study. One death was associated with the absorption of an excessive amount of adrenalin applied locally during a four and one-half hour period in an attempt to control bleeding during an operation on the frontal sinus. Throughout the procedure the systolic blood pressure of the patient rose steadily from 120 to 200 and was associated with a steady increase in the pulse rate.

It is immediately apparent that an important consideration in determining the incidence of operative deaths is the number of seriously ill patients requiring operation. This number is greatest in hospitals in large cities when the hospitals maintain an active accident clinic where many serious emergency cases requiring immediate operation are admitted, and in hospitals which admit many acutely ill patients, some of whom require operative procedures even when in a critical condition.

ANALYSIS OF THE DEATHS APPARENTLY RELATED TO THE ANESTHESIA

Twenty deaths appeared to be related to the anesthesia or to the care of the patient during the administration of the anesthetic agent. The chief apparent factor in the death of 4 patients was obstruction of the main respiratory passages; 3 patients died in association with

the administration of spinal anesthetic agents; one died as the result of an explosion; 3 deaths seemed possibly to be attributable to some error in the administration of an inhalation anesthetic agent; and in 9 instances there was no adequate explanation (Table II). The case records of these 20 patients are summarized.

Edema of the larynx and epiglottis. One patient with hemophilia was admitted to the operating rooms through the accident clinic with a hematoma of the sublingual and parotid area following the extraction of a tooth. Cauterization of the tooth socket was deemed imperative. Although aware of the hazards, the operator decided to use a general anesthetic because he felt that the patient was too uncooperative for

TABLE II

Factors in the deaths apparently associated with the anesthesia

		DEATHS
Obstruction of the main respiratory passages	Edema of the larynx	1
	Aspiration of regurgitated gastric contents	3
"Spinal deaths"		3
Explosion		1
Technique of administration of the anesthetic agent		3
No adequate explanation		9
Total		20

the procedure to be carried out under local anesthesia. Pentothal sodium was administered intravenously. A rubber catheter was passed through the nostril presumably into the trachea, but it may have reached only to the pharynx. Fifteen minutes after the anesthesia was started the respirations became jerky as if impeded, and the administration of the anesthetic agent was stopped. Twenty-five minutes later respirations ceased, and death was found to be due to obstruction of the larynx by edema.

Obstruction of the main respiratory passages by aspirated gastric contents regurgitated during the anesthesia resulted in 3 fatalities. One patient in good general condition was admitted to the operating rooms directly from the accident clinic with a gunshot wound of the abdomen. His stomach was not emptied before the administration of the anes-

thetic. During the administration of nitrous oxide-oxygen before the operation was begun he vomited and aspirated a bolus of food with immediate cessation of respirations. Tracheotomy was unsuccessful in providing a clear airway.

A very obese woman had had on the day before operation an attack of sudden syncope with a considerable fall in blood pressure from which she had rapidly recovered. The following day signs of intestinal obstruction developed and an exploratory laparotomy was performed under nitrous oxide-oxygen-ether anesthesia. Anesthesia was difficult because of poor respiratory exchange. During the induction with nitrous oxide she vomited undigested food, and during the rest of the anesthesia she regurgitated gastric contents frequently. When the operation was nearly finished respirations ceased, and at autopsy the larynx was found to be almost completely occluded by gastric contents. There was also a fresh thrombus in the right pulmonary artery, probably associated with the attack of syncope the day before operation.

The last patient in this group was a man with a ruptured spleen who was taken to the operating rooms directly from the accident clinic. His stomach was not emptied before the administration of the anesthetic. He had nitrous oxide-oxygen induction followed by ether anesthesia. During the abdominal exploration and intestinal manipulation there was regurgitation of gastro-intestinal contents which were aspirated with resulting death. This occurred twenty-five minutes after the start of the anesthesia.

Deaths associated with spinal anesthesia. In this series there were 3 fatalities associated with the administration of spinal anesthetic agents. One patient was a short, obese woman with slight hypertension who was given a solution heavier than spinal fluid (pontocaine[1] 12 mgm. in 5 per cent glucose solution). There was almost immediate anesthesia reaching to the costal margin, respiratory distress, and shock. Intermittent insufflation of oxygen was instituted immediately, but death occurred forty minutes later with cessation of the heart beat.

An elderly woman with diabetes mellitus and hypertension received 125 mgm. of procaine[2] intraspinally for the amputation of a leg for diabetic gangrene. Twenty-five minutes later her systolic blood pressure fell from 200 to zero, and she expired with sudden cessation of respirations.

[1] Pontocaine hydrochloride.
[2] Procaine hydrochloride.

The third death occurred in a woman seventy-eight years of age who had hypertension and was in poor condition as the result of an intestinal obstruction. Three minutes after being given pontocaine (20 mgm. in 2 cc. of spinal fluid) her systolic blood pressure fell to 50 and she died with sudden cessation of respirations, the blood pressure having continued to fall rapidly to zero.

Explosion. An explosion caused the death of one patient on whom there was being performed an incision of a large carbuncle of the neck under nitrous oxide-oxygen-ether anesthesia. Only a small quantity of ether was used, and the anesthetic mixture was highly explosive. Numerous bleeding points were encountered in the operative field, and the electric cautery was to be used to control them. At the first application of the cautery the anesthetist, who was in direct contact with the patient, felt a sharp electrical impulse and jumped back from the operating table. This movement allowed the anesthetic mask to come off the patient's face, and almost immediately an explosion occurred which was fatal to the patient. The exact mechanism by which the accident had occurred could not be determined.

The technique of administration of an inhalation anesthetic agent appeared to have been a factor in the death of 3 patients. One patient with hypertension and a history of angina pectoris received nitrous oxide-oxygen for the induction followed by a small amount of ether for an appendectomy. After fifteen minutes of anesthesia respirations suddenly ceased. In retrospect it seemed that perhaps the patient at no time was allowed sufficient oxygen, and that death might have been due to anoxemia. This patient has been reported by Follis (2) as having died under anesthesia with associated stenosis of the coronary arteries.

A young man undergoing resection of a duodenal ulcer had nitrous-oxide anesthesia supplemented by a celiac block with 80 cc. of pontocaine solution (1:3000) containing adrenalin. Sudden cessation of respirations occurred one hour and forty-five minutes after the beginning of the anesthesia, the nitrous oxide having been administered in a closed system by the carbon-dioxide absorption technique. The oxygen in the system was apparently kept at a level sufficient for the basal needs of the patient. Subsequent investigation, however, revealed that an inaccuracy in the flow meter had resulted in 20 per cent

less oxygen being present than was intended. This death under anesthesia has been reported previously (2) because the patient had stenosis of the right coronary artery as learned at autopsy, but slight anoxemia maintained over a long period of time must be considered as a possible factor in the death.

The third patient was a young man in good condition on whom a tonsillectomy was being performed under ether anesthesia following induction with nitrous oxide-oxygen. A Davis mouth gag was used. From the beginning the anesthesia was unsatisfactory, the respirations were gasping, the patient was cyanotic, and the relaxation poor. After one hour of anesthesia, during which time the patient received six ounces of ether, respirations ceased. Possibly this death might have been avoided had the operation been delayed until a satisfactory anesthetic state could be obtained.

No definite explanation could be found for 9 deaths, although the poor preoperative condition of the patients was thought to be a contributing factor in the sudden death of 4 of them. However, the preoperative condition of these patients was not such as could be justifiably accepted as the sole cause of death as was the case in many of the group previously discussed as non-anesthetic deaths. In a colored male forty-five years of age who was about to undergo an abdominal exploration for perforation of the gallbladder, anesthesia was induced with nitrous oxide. Just as this was being supplemented with ether the patient sat up suddenly, took several labored breaths, and died with abrupt cessation of the heart beat. This fatality has been reported (2) as a sudden death under anesthesia associated with stenosis of the right coronary artery. This explanation is probably the correct one since the anesthesia was so light that the patient could sit up on the table, and hence death could not have been due to too deep an anesthetic level.

A colored male thought to have aortic insufficiency but considered a good anesthetic risk died suddenly at the completion of an easily performed section of the trigeminal nerve carried out through a cerebellar approach. The operation was performed under avertin basal anesthesia supplemented with inhalation ether anesthesia. Death occurred one hour after anesthesia was started. At the time of death the question was raised whether pressure on the lower part of the

patient's neck from a poor position on the table was the precipitating factor. Autopsy showed cardiac hypertrophy, generalized arteriosclerosis, and coronary sclerosis. The cause of death was not entirely clear, but the diseased condition of the heart may have been partly responsible.

The third patient was a colored man sixty years of age who had syphilitic aortitis and epilepsy in whom reduction of a fracture of the mandible was being attempted. Following nitrous oxide-oxygen induction the patient received seven and one-half ounces of ether. Much mucus was present in the upper respiratory tract of the patient during the first part of the anesthesia. Respirations ceased sixty-five minutes after the start of the anesthesia and twenty-one minutes after operative manipulation of the fractured mandible had been begun. With artificial respiration and the administration of coramine intravenously respirations were resumed. Fifteen minutes later the respirations again ceased, and this time could not be restored. At autopsy there was found syphilitic aortitis, generalized arteriosclerosis, and encephalomalacia. The sequence of events in this case was difficult to understand.

A colored female with hypertension who was suffering respiratory embarrassment from a huge intra-abdominal tumor underwent an exploratory laparotomy under drop-ether anesthesia. Just as the tumor was being delivered the respirations suddenly ceased. It was felt by the operator and the members of the gynecological staff that death was due to the effects of deep ether anesthesia in a patient whose poor condition did not enable her to withstand the shock of the sudden removal of such a large intra-abdominal mass. In this case, too, the cause of death is not entirely clear.

Five deaths were classified as "anesthetic deaths" because there was no other apparent cause, but it could not be determined definitely from the case records that all were true anesthetic deaths. A young man under study in the hospital for epilepsy was operated on for volvulus, the procedure being performed under avertin basal anesthesia supplemented with nitrous oxide-oxygen inhalation anesthesia. After an hour of anesthesia the respirations suddenly ceased without apparent cause.

In a white woman in good physical condition one external carotid artery was ligated preparatory to operation upon a tumor of the jaw. She had avertin basal anesthesia supplemented by open-drop ether. The color and respirations of the patient remained good during an hour and forty-five minutes of anesthesia, but just as the incision in the neck was being closed she inexplicably became cyanotic and ceased breathing.

A very obese white woman with hypertension, a large adenoma of the thyroid gland, and a normal basal metabolic rate was operated on under open-drop ether anesthesia. The thyroid gland was removed without difficulty, but as the incision was being closed two and one-half hours after anesthesia had been begun the blood pressure of the patient fell appreciably. Intravenous fluids were administered, but the respirations ceased abruptly a few minutes later while the heart beat continued for a short time longer. In this case the operator did not raise the question of an anesthetic death, but suggested that death might have been due to some peculiar central reflex. Certainly the cause of death was not clear, and the anesthesia could not be excluded as a possible factor.

A puzzling case was that of a girl fourteen years old and in excellent physical condition in whom a portion of a rib was excised for grafting to the mandible. She had received avertin basal anesthesia supplemented by inhalation ether administered by means of an intrapharyngeal catheter. During the resection of the rib a small tear was made in the pleura, but this was recognized and closed, and the small pneumothorax had no apparent effect upon the respirations. After two and one-half hours of anesthesia the respirations suddenly ceased. Autopsy failed to provide an adequate explanation for the death.

The last patient in this group was a woman with well regulated hyperthyroidism who was operated on under avertin basal anesthesia supplemented by inhalation ether administered by means of an intratracheal catheter. Thyroidectomy was accomplished without difficulty, and the intratracheal catheter was removed as the incision was being closed. Immediately thereafter respirations suddenly ceased while the heart beat remained good. Prompt tracheotomy revealed a clear airway, and autopsy examination furnished no explanation.

DISCUSSION

Possibly avoidable deaths. Analysis of the 20 fatalities apparently related to the anesthesia or to errors in the technique of administration of the anesthetic agents suggested that 11 possibly could have been avoided (Table III). These cases have been described in detail. In one report (3) in the literature there were discussed 9 deaths which occurred on the operating table, and the conclusion was reached that 2 of these definitely could have been avoided. In the present series the most conspicuous of the deaths which might possibly have been avoided was the one resulting from an explosion. It is of note that this was the only anesthetic explosion to occur in the Johns Hopkins Hospital in 47 years, during which period an estimated 200,000 anes-

TABLE III

Factors in the possibly avoidable deaths

	DEATHS
Edema of the larynx and epiglottis	1
Obstruction of main respiratory passages by aspirated gastric contents	3
Explosion	1
Technique of administration of the anesthetic agent	3
"Spinal deaths"	3
Total	11

thetics with inhalation gaseous anesthetic agents were administered. Reports in the literature would suggest that anesthetic explosions have been more frequent than might be supposed. An editorial in the Journal of the American Medical Association (4) estimated explosion accidents as 100 a year. Guedel (5) reported 3 cases of oxygen-ether explosions. Sise (6) reported one explosion in 40,000 cyclopropane anesthesias. The results of questioning one hundred leading anesthetists concerning explosions were published by Woodbridge (7) who reported an incidence of two to four-explosions per 100,000 anesthesias. The explosion reviewed in the present report, as has been described, occurred in the presence of an electric cautery. Greene (8), in reviewing 230 explosions, found that 40 per cent occurred in the presence of electrical machines.

The 4 deaths in which obstruction of the respiratory passages was a factor might possibly have been avoided. In 3 instances the patients were admitted to the operating rooms for emergency operative procedures (2 of these patients were admitted directly from the accident clinic), and their stomachs had not been emptied before the administration of the inhalation anesthetic. All 3 patients aspirated gastric contents regurgitated during the anesthesia, and died with obstruction of the main respiratory passages by the aspirated material. These fatalities would suggest that greater care might be taken in the preparation of patients for emergency operations under general anesthesia.

In the case of the patient dying with respiratory obstruction due to edema of the larynx it would appear that since the operator considered a general anesthesia necessary, it was imperative that a clear airway should be assured. Williams and Marcus (9) urge that in operations performed on patients with Ludwig's angina the patient be prepared for tracheotomy regardless of the type of anesthesia to be used. They advise that this preparation take the form of dividing under local anesthesia all the structures of the neck so as to expose the tracheal cartilages. We feel that in any case where there exists a phlegmonous inflammatory process in the region of the pharynx, larynx, or trachea and the respirations are precarious and maintained by the accessory muscles of respiration, a clear airway must be made certain regardless of whether a local or a general anesthetic agent is to be used, even if such an airway necessitates a tracheotomy. It is our feeling that in such cases local anesthesia without preliminary sedation should be used.

Factors in 3 fatalities which might perhaps have been avoided were possible errors associated with the technique of administration of an inhalation anesthetic agent. These cases are described in a preceding paragraph, as are the 3 deaths related to spinal anesthesia. In these three instances of "spinal deaths" the details of administration of the anesthetic agent were not set down in the case records; hence it could not be determined whether or not these deaths were explicable on the basis of faulty technique. It is possible, for example, that the drugs might have been injected too forcefully and rapidly, or in too large a quantity of fluid. In the case of the patient upon whom a leg amputation was to be performed there was need for only a very low anes-

thetic level—far too low to affect the accessory muscles of respiration. In the case of the woman seventy-eight years of age, who underwent an exploratory laparotomy for intestinal obstruction, it would appear that the choice of the type of anesthesia might have been open to question since the patient was elderly and acutely ill and had hypertension. The dose of pontocaine was possibly excessive for one of her age and physical condition. The occurrence of an immediate anesthetic level as high as the costal margin in the case of the obese patient given intraspinally an anesthetic solution heavier than spinal fluid would suggest that the anesthetic mixture had been injected too forcefully. It is of interest to note that all three of these patients had hypertension, and that two of them were in poor general physical condition.

Apparently unavoidable deaths. The 9 deaths for which no adequate explanation could be found were classified as unavoidable, and have been outlined in detail. As has been stated, it was impossible from the available data to determine whether these were all true "anesthetic deaths"; but in the absence of any satisfactory cause of death being found they must be called unavoidable. Many possible explanations for such fatalities under anesthesia have been suggested. For example, there is the experimental work of Downs (10) who anesthetized dogs with nitrous oxide and found on compression of the carotid sinus that in one half of the dogs there was sudden cessation of respirations in addition to the expected transitory fall in blood pressure. He suggested this phenomenon as one possible explanation for the cerebral anoxemia in cases of otherwise unexplained sudden death under anesthesia. Lundy (11) stated that under light anesthesia with intravenous pentothal sodium, stimulation of an inflammatory lesion may affect the carotid sinus reflex and cause cessation of the heart beat. In some cases where autopsy revealed no apparent cause of death Davis (12) suggested reflex syncope and laryngospasm as a possible explanation.

Mortality rates. In the present series of deaths under anesthesia there was an average distribution of cases during the decade studied, and in no one year was there a preponderance of deaths. In each instance the anesthetic agent had been chosen by the operator as the one supposedly the best suited to the individual patient in relation to the operative procedure to be carried out. In the 51,392 anesthesias,

general and spinal, there was a mortality in the operating room of 1.5 per 1000. Kaye (13) reported an incidence of deaths on the operating table of 1.8 per 1000 in 13,400 operations performed between 1919 and 1929, and an incidence of 1.3 per 1000 in 17,757 operations performed between 1929 and 1934. The gross anesthetic mortality rate in the present group of cases studied was 0.039 per cent. The mortality rates for the various anesthetic agents with which death occurred, as discussed in this analysis, are recorded in Table IV. With these

TABLE IV

Mortality rates with the various anesthetic agents with which deaths occurred

	NUMBER OF ANESTHESIAS	NUMBER OF "ANESTHETIC" DEATHS	PER CENT MORTALITY
Total number of general and spinal anesthetics administered from July 1, 1931 to July 1, 1941	51,392	20	0.039
Nitrous oxide-oxygen-ether	15,206	5	0.033
Open drop ether alone	3,456	2	0.057
Spinal anesthesia alone	4,010	3	0.075
Avertin basal anesthesia supplemented by inhalation ether	8,149	2	0.024
Avertin basal anesthesia supplemented by inhalation nitrous oxide-oxygen	3,483	1	0.029
Avertin basal anesthesia supplemented by inhalation nitrous oxide-oxygen-ether	1,300	2	0.150
Nitrous oxide-oxygen*	4,398	4	0.091
Pentothal sodium intravenously	1,706	1	0.058

* Two patients in the nitrous oxide-oxygen group received less then one-half ounce of ether.

different agents the rate varied from 0.024 per cent to 0.091 per cent, the differences between the various percentages being statistically unimportant. Avertin basal anesthesia supplemented with inhalation nitrous oxide-oxygen-ether anesthesia was an exception, the mortality rate of 0.15 per cent being greater than average. These figures do not represent total results because they do not include all the anesthetics administered during the decade studied, those given in the emergency-out-patient clinic and in the obstetric and opthalmologic operating rooms having been omitted as explained previously. They do repre-

sent, however, the material concerning which adequate information was available. These mortality rates do not differ greatly from those reported by many investigators (13, 14, 15, 16, 17, 18, 19), and are lower than those reported by some (20, 21).

The immediate anesthetic mortality is admittedly only one of very many important factors. The anesthetic agent with the lowest mortality rate is not necessarily the safest; and the best anesthetic agent for one procedure may be the poorest choice for another. The proper level of anesthesia and the degree of relaxation undoubtedly influence the ease and technical perfection of the operative procedure, and thus contribute to both the ultimate success of the operation and to such important matters as operative trauma, shock, postoperative distension, fluid and food intake, proper bladder and bowel evacuation, and other reactions of the patient. Conversely, the anesthetic agent and the anesthetist are not the only factors in satisfactory anesthesia. The surgeon can, by cooperation and gentle technique, make the administration of the anesthetic easy; or he can make it very difficult. A most important consideration in the evaluation of any anesthetic agent is the interrelation of preoperative preparation and condition of the patient, anesthesia and operation, and ultimate result. Unfortunately an analysis of ordinary case records is inadequate for such a broad study. It is hoped that the present more limited analysis may serve to point out some of the factors concerned in immediate anesthetic mortalities.

SUMMARY

The authors have reviewed the records of patients to whom 51,392 general anesthetic agents and spinal anesthetic agents were administered in the Johns Hopkins Hospital between July 1, 1931 and July 1, 1941, in order to determine the incidence and causes of deaths in the operating rooms when such anesthetics were used.

There occurred 75 deaths, an incidence of 1.5 deaths per 1000 anesthesias. Fifty-five deaths (73.3 per cent) were definitely unrelated to the anesthesia, and 20 (26.7 per cent) seemed to be related to the anesthesia. However, there was found no single causative factor for the deaths; and no death could be attributed exclusively to the anesthetic agent *per se*.

Of the 20 deaths apparently related to the anesthesia, 9 seemed unavoidable, no adequate explanation having been found; 11 might possibly have been avoided. Of these 11 deaths, 4 resulted from obstruction of the main respiratory passages: one from edema of the larynx, and 3 from aspiration of gastric contents regurgitated during the administration of inhalation anesthetic agents to patients undergoing emergency operations and whose stomachs had not been emptied before the administration of the anesthetic. These deaths would suggest that greater care might be taken in preparing patients for emergency operations under general anesthesia.

One death resulted from an explosion, the only explosion occurring in the hospital in 47 years, a period of time in which an estimated 200,000 inhalation anesthetic agents were administered.

Three deaths related to the anesthesia appeared to have been associated with the technique of administration of an inhalation anesthetic agent. Three additional deaths were related to the administration of spinal anesthetic agents.

The gross anesthetic mortality rate in the operating rooms was 0.039 per cent, and there were no statistically significant differences between the mortality rates with the various anesthetic agents. When the possibly avoidable deaths were excluded and only those were considered for which no adequate explanation could be found, there was an anesthetic mortality rate of 0.017 per cent.

REFERENCES

1. SHUMACKER, H. B., JR.: Reactions to local anesthetic agents: clinical report. *Surgery*, **10:** 134, July, 1941.
2. FOLLIS, R. H., JR.: Coronary arteries in relation to sudden death during anesthesia (nitrous oxide, oxygen, and ether). *Bull. Johns Hopkins Hosp.* **67:** 211, Sept. 1940.
3. Anonymous: Anesthetic failures. *M. J. Australia*, **2:** 866, Dec. 21, 1935.
4. Editorial: An anesthetic accident. *J. A. M. A.*, **92:** 476, Feb. 9, 1929.
5. GUEDEL, A. E.: Oxygen-ether explosions: three case reports. *Current Researches in Anesth. and Analg.*, **2:** 138, Aug., 1923.
6. SISE, L. F.: General anesthesia. *New Eng. J. Med.*, **220:** 667, April 20, 1939.
7. WOODBRIDGE, P. D.: Incidence of anesthetic explosions. *J. A. M. A.*, **113:** 2308, Dec. 23, 1939.
8. GREENE, B. A.: The hazards of fire and explosions in anesthesia. *Anesthesiology*, **2:** 144, March, 1941.

9. WILLIAMS, A. C., AND MARCUS, P. S.: The choice of anesthesia in Ludwig's angina. *Anesth. and Analg.*, **20:** 160, May–June, 1941.
10. DOWNS, T. McK.: The carotid sinus as an etiological factor in sudden anesthetic death. *Ann. Surg.*, **99:** 974, June, 1934.
11. LUNDY, J. S.: A technical description of the intravenous administration of pentothal sodium based on experience in more than 12,500 administrations. *J. Canad. Dent. Ass.*, **5:** 589, Nov., 1939.
12. DAVIS, F. E.: Laryngospasm and its relation to anesthesia. *Bull. Nat. Ass. Nurse Anesthetists*, **7:** 155, Aug., 1939.
13. KAYE, J.: Anesthetic deaths in Melbourne, 1929–1934. *Brit. Jour. Anesthesia*, **13:** 110, April, 1936.
14. KEEN, quoted by EVANS, J. H.: Ether and nitrous oxide-oxygen anesthesia. *N. Y. State J. Med.*, **32:** 125, Feb., 1932.
15. PANGMAN, W. J.: Avertin tribromethanol as basal anesthetic. *Southwestern Med.*, **22:** 6, Jan., 1938.
16. SCHMIDT, E. R., AND WATERS, R. M.: Cyclopropane anesthesia; postoperative morbidity in 2200 cases. *Current Researches in Anesth. and Analg.*, **14:** 1, Jan.–Feb., 1935.
17. DRAPER, W. B., AND WHITEHEAD, M. A.: The acute safety of ether, divinyl ether, and chloroform in the production of the "obstetric degree" of analgesia. *Surg., Gyn., and Obst.*, **67:** 436, Oct., 1938.
18. BRENNAN, H.: Concerning spinal analgesia: 2 pertinent cases and criticism. *Brit. J. Anesth.*, **15:** 147, July, 1938.
19. GIORDENANGO, G.: Incidente e complicazioni gravi da anestesie spinali. *National Congress of the Italian Society of Anesthesia and Analgesia*, **5:** 67, Oct., 1936.
20. BABCOCK, M. E.: Spinal deaths, a survey. *Anesth. and Analg.*, **11:** 184, July–Aug., 1932.
21. EMMETT, J. M.: Fourteen-hundred and fifty spinal anesthesias with special reference to indications, complications, and mortality. *Virg. Med. Monthly*, **62:** 304, Sept., 1935.

DIFFICULTIES IN THE ENZYMIC TITRATION OF DUODENAL CONTENTS

WILBURT C. DAVISON

From the Departments of Pediatrics of the Johns Hopkins and Duke University Schools of Medicine

Submitted for publication January 26, 1942

Georges Dreyer once said that publication should not be attempted until at least ten years after the experiments had been done. These have waited fifteen years, partly from procrastination, partly because these rather negative results do not advance the subject, and partly because the interest in this field was dormant. However, Andersen's excellent papers this year (1) have re-opened the subject, and other reports probably will be published. Therefore these discouraging comments are being recorded to save others the same disappointments, and also to warn them not to place too much faith in quantitative enzymic titrations. Gross differences in average titrations of enzymic activity, such as those reported by Andersen, (1) as well as those which occur during diarrhea (2, 3) (Table I), are significant if they are at least three times the Standard Error (see below), but "caveat opifex" to anyone who uses methods with as many pitfalls, stumbling blocks, variables, etc. as are encountered in enzymic titration.

These difficulties are illustrated by the results of 9 trypsin titrations and 11 amylase measurements of 5 specimens of the duodenal contents of an infant during and after an attack of diarrhea, and 67 trypsin and 72 amylase determinations of 30 specimens of duodenal contents from 9 infants with normal digestion. The method of collection of duodenal contents has been described elsewhere (2, 3). The enzymic activity of these duodenal contents, unless otherwise stated, was determined quantitatively at frequent intervals by measuring with a stop-watch the time required for 5 cc. of a mixture of duodenal contents and 3 per cent gelatin at pH 7.4 (trypsin) (4) or 2.5 per cent starch solution at pH 7.0 (amylase) (5) to flow through the capillary tube of an Ostwald viscosimeter in a water bath at 34° C.

The following are some of the factors which often are responsible for

TABLE I

TABLE I

Relation of duodenal trypsin and amylase values to the state of digestion, using viscometric titration at 34° C. with 3% gelatin at pH 7.4 for trypsin (4) and 2.5% starch at pH 7.0 for amylase (5)

PATIENT AND DATE OF SPECIMEN*	SPECIMEN NUMBER AND (HOURS AFTER LAST MEAL)	TRYPSIN				AMYLASE			
		Date of titration	Amount (and dilution) of duodenal contents used	Time required for 20% reduction in initial viscosity	Trypsin units per cc. of duodenal contents	Date of titration	Amount (and dilution) of duodenal contents used	Time required for 20% reduction in initial viscosity	Amylase units per cc. of duodenal contents
During acute diarrhea									
			cc.	*min.*			*cc.*	*min.*	
No. 1; 11/4	I (5)	11/4	0.1 (undil.)	165	3.6	11/4	0.1 (1:7.5)	19	236
						11/4	0.1 (undil.)	3	200
						11/4	0.1 (1:7.5)	20.25	222
									219.3 (av.)
	II (6)	11/4	0.1 (undil.)	111	5.4	11/4	0.1 (1:7.5)	37	121
						11/4	0.1 (1:7.5)	25	180
									150.5 (av.)
1 Month later; after recovery of normal digestion									
No. 1; 12/3	III (6)	12/3	0.1 (1:3)	22.7	79.2	12/3	0.1 (1:12.5)	15.5	456
		12/4	0.1 (1:7.5)	53.6	84.	12/4	0.1 (1:7.5)	10.75	401.8
		12/4	0.1 (undil.)	6.3	95.2				428.9 (av.)
					86.1 (av.)				
	IV (7)	12/3	0.1 (1:3)	19	94.8	12.3	0.1 (1:12.5)	11.5	652
		12/4	0.1 (1:3)	16.6	108.4	12.4	0.1 (1:12.5)	8	937.5
					101.6 (av.)				794.7 (av.)
	V (8)	12/3	0.1 (1:3)	26	69.2	12/3	0.1 (1:12.5)	13.2	568
		12/4	0.1 (1:3)	24	75.	12/4	0.1 (1:12.5)	10.75	698
					72.1 (av.)				633 (av.)

* The clinical data are published elsewhere (3).

the inaccuracies in the reports of the enzymic activity of duodenal contents:

1. *Calculation of enzymic units:* Of the various methods which have been used (1, 6), the measurement of changes in viscosity described by Northrop and Hussey (4) has the advantage of simplicity. The successive measurements of viscosity must be plotted in order to determine the rate of change, since the time required to produce a definite amount of change is inversely proportional to enzymic activity; e.g., if 0.1 cc. of an enzyme preparation requires 60 minutes to reduce the initial viscosity 20 per cent, 0.2 cc. reduces it a similar amount in 30 minutes (4). On the other hand, the amounts of change in a definite time are not proportional; e.g., regardless of the strength of the enzyme, the viscosity of gelatin or starch suspensions to which different amounts of enzyme have been added, usually but not always, fall to that of the buffer mixture in 2 to 12 hours. As the strength of an enzyme is inversely proportional to the *time* required to effect a definite percentage of change in the viscosity of the substrate but not to the *amount* of change in a definite period of time, Northrop and Hussey (4) defined a unit of trypsin as that amount of enzyme which required 60 minutes to produce a 20 per cent reduction in the viscosity of the substrate. An amylase unit is similarly defined (5). For example, if 0.1 cc. of duodenal contents reduces the initial viscosity 20 per cent in 60 minutes it contains 1 unit or 10 units per cc. Again, if 0.2 cc. reduces the initial viscosity 20 per cent in 30 minutes, it contains 2 units or 10 units per cc. If 20 minutes is required to reduce the initial viscosity 20 per cent, the material being tested would contain 60/20 or 3 units, etc. Sixty minutes and a 20 per cent change were used to define a unit as faster rates were difficult to determine accurately: the frequent measurements of viscosity consume 1–2 minutes each and the enzymic activity continues during the observations. Slower rates permit bacterial growth and allow other sources of errors to develop. Side reactions, which affect the viscosity, occur with changes greater than 20 per cent in the substrate.

Viscosity determinations in enzymic measurements can be plotted against time in four ways: (1) As the "observed" viscosity (η, the outflow time of 5 cc. of the gelatin- or starch-enzyme mixture), (2) the "net" viscosity ($\eta - \eta_0$ (the outflow time of the buffer solution)), (3) the

"relative" viscosity (η/η_0), and (4) the "specific fluidity" ($\eta_0/\eta-1$). The resulting curves have the same general shape, and as the first method is simpler and as accurate as the other three (7), it was used in determining the number of units per cc. of duodenal contents in the enzymic titrations in this paper. On the basis of this "observed" viscosity, the average number of trypsin units per cc. of the enzymic titrations in Fig. 1 was 55. As Northrop and Hussey stated (4), the

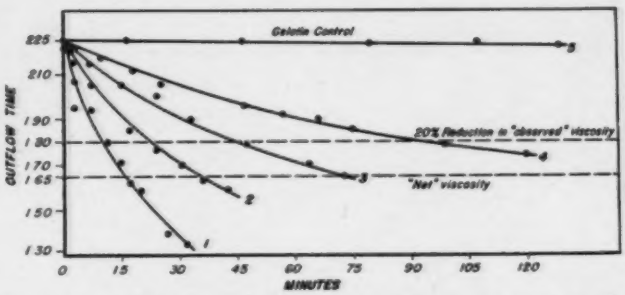


FIG. 1. *Trypsin titrations* plotted from the changes caused in the "observed" viscosity of 10 cc. 3 per cent gelatin at pH 7.4 and 34°C. by 0.1 cc. of enzyme (courtesy of Drs. J. H. Northrop and R. G. Hussey).[4]

CURVE	DILUTION OF 0.1 CC. ENZYME	MINUTES REQUIRED FOR A 20% REDUCTION IN THE "OBSERVED" VISCOSITY	TRYPSIN UNITS PER CC. OF ENZYME
1	Undiluted	10.2	59 (60/10.2 × 10)
2	1:2	21.3	56 (60/21.3 × 2 × 10)
3	1:4	44.9	53 (60/44.9 × 4 × 10)
4	1:8	92.4	52 (60/92.4 × 8 × 10)

values shown in Fig. 1 varied as the reciprocal of the relative amounts of trypsin used with only 5± per cent error; i.e. double the amount required half the time to cause the same change (Arrhenius' "QT" rule). The maximum percentage-difference error (see below) in the number of units per cc. calculated on the basis of a 20 per cent reduction in the "observed" viscosity was 7.3 (4 (maximum difference from the average) ÷ 55 (average)).

The results obtained were plotted on coordinate paper, the abscissae

representing the elapsed time between measurements of the viscosity of the gelatin—or starch—enzyme mixtures, and the ordinates the "observed" viscosities expressed as percentages of the initial "observed" viscosity. For example, in Curve 7 of Fig. 2, the outflow time of the starch-enzyme mixture at the time of adding the duodenal contents, or initial "observed" viscosity, was 107.4 seconds, and was represented on the ordinate scale as 100 per cent (abscissa scale 0 min.) The "observed" viscosity of the starch-enzyme mixture 10

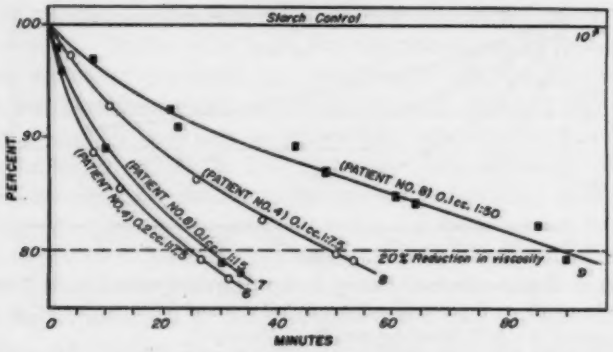


FIG. 2. *Amylase titrations* (*Table 4*). Curve 6 was plotted from the changes caused in the viscosity of 10 cc. 2.5 per cent starch at pH 7.0 and 34°C. by 0.2 cc. duodenal contents (diluted 1:7.5 with normal saline) from patient No. 4. Curve 8 represents the amylase activity of 0.1 cc. of the same specimen (diluted 1:7.5). Curve 7 indicates the amylase activity of 0.1 cc. duodenal contents (diluted 1:15) from patient No. 8, Curve 9 that of 0.1 cc. of the same specimen (diluted 1:50), and Curve 10 that of the starch control (without duodenal contents).

minutes after adding the duodenal contents, which was 96 seconds, was plotted on the ordinate scale as 89 per cent, i.e., 107.4:100 = 89:x, and x = 89; the abscissa was 10 min. This apparently complicated, though really simple, slide-rule method of recording results was necessitated by the fact that, since several different viscosimeters usually were used, the initial "observed" viscosities frequently were not the same and, therefore, had to be reduced to the same scale (5); e.g., in curves 6 to 9 in Fig. 2, in which different viscosimeters were used, the initial "observed" viscosities or outflow times were 114, 107.4, 107.7 and 59.4 seconds respectively.

2. *Enzyme methods:* The viscometric titration of trypsin (4) and amylase (5), which was used in this study, is simpler and more accurate than most enzyme methods (8), except for Anson's hemoglobin estimation (9), which is more exact and convenient. Enzymes are measured by the rate of change they produce rather than by a given end-point as in other chemical determinations, and therefore errors are more likely to occur, even when all of the determinations are made by the same individual. As shown in Table II, parallel determinations rarely gave the same result, so averages of several titrations were used. But even averages of parallel titrations were far from accurate. In order to gauge the reliability of the 159 enzymic titrations on which this paper is based, the results of the parallel titrations of trypsin and amylase were separated into three groups: (1) Those using the same amounts of the same specimen (Table II), (2) those using different amounts and different dilutions of the same specimen, and (3) those using fresh and 24 hour-old specimens of the same duodenal contents. In these three groups, the following calculations were made: (a) The average of the units in each set of parallel titrations, (b) the difference between the units in each of the parallel titrations, and (c) the percentage-difference, obtained by dividing each average into each difference. This last figure was used as the criterion of accuracy of the titrations.

As may be seen in Table III, these percentage-differences of the parallel titrations varied from 0.16 to 166, and the mean percentage-differences from 11 to 61. Parallel titrations with percentage-differences of less than 20 probably are as accurate as can be obtained with the viscometric method. Measurements made with the same amounts of the same specimen (Table II), as would be expected, were more reliable than were the number of units calculated from titrations using different amounts and different dilutions of the same specimen, or from measurements of fresh and 24-hour-old specimens of the same duodenal contents. The amylase titrations were more accurate than those for trypsin, i.e., a larger proportion of the parallel titrations of amylase had percentage-differences of less than 10. Two parallel titrations of the amylase of duodenal contents with a percentage-difference of 1.4 and 2.1 are illustrated in Fig. 2. and Table IV.

The reliability of enzymic titrations may be gauged more precisely by calculating the Standard Deviation and Standard Error. In

TABLE II

Comparison of parallel titrations of the trypsin and amylase activity of the same amounts of the same specimens of duodenal contents

TRYPSIN						AMYLASE					
Patient and (specimen)	Units		Average	Difference	Percentage difference	Patient and (specimen)	Units		Average	Difference	Percentage difference
	1st titration	2d titration					1st titration	2d titration			
3 (I)	150	250	200	100	50	1 (I)	222	236	229	14	6
3 (III)	79	115.2	97.1	36.2	37	1 (II)	121	180	150.5	59	39
7 (II)	196	203	199.5	7	3.5	3 (II)	146.5	171.5	150	25	16
7 (III)	108	125	116.5	17	15	3 (IV)	311	316	313.5	5	1.6
8 (I)	78.2	94.8	86.5	16.6	19	5 (II)	631	667	649	36	5.5
8 (III)	96.3	155	125.6	58.7	47	5 (III)	631	667	649	36	5.5
8 (IV)	132.2	138.4	135.3	6.2	4	7 (I)	558	595	576.5	37	6
8 (V)	353	392	372.5	39	10.5	7 (II)	638	652	645	14	2
9 (III)	117.5	171.5	144.5	54	37	7 (II)	750	856	803	106	13
10 (I)	265	298	280	29	10	7 (III)	736	945	840.5	209	25
						8 (III)	392	401.8	396.9	9.8	2.5
						8 (IV)	474	530	502	56	11
						9 (I)	674	760	717	86	12
						9 (IV)	692*	750*	721	58	8
						9 (V)	211†	237†	224	26	11
Total.....	1,575.2	1,942.9	1,757.5	363.7	19 (mean)	Total.....	7,187.5	7,964.3	7,566.9	776.8	11 (mean)
Standard deviation = 94.86; standard error = 19.6.						Standard deviation = 196; standard error = 36.					

* Both titrations at 36°C.

† Both titrations at 35°C.

Table II, the variants of the parallel titrations of the trypsin and amylase activity of the same amounts of the same specimens of duodenal contents have been analyzed. The Standard Deviation was calculated as the square root of the difference between the sum of the squares of the individual determinations and the square of the sum of all the determinations, divided by the total number of parallel determinations. The Standard Error is the Standard Deviation divided by the square root of the total number of parallel titrations.

TABLE III

Percentage of accuracy in parallel titrations of the trypsin and amylase activity of duodenal contents

PERCENTAGE DIFFERENCE	TRYPSIN			AMYLASE		
	1. Using the same amounts of the same specimen	2. Using different amounts and different dilutions of the same specimen	3. Using fresh and 24 hr.-old specimens	1. Using the same amounts of the same specimen	2. Using different amounts and different dilutions of the same specimen	3. Using fresh and 24 hr.-old specimens
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
0.16–10	27*	8*	15*	47*	32*	0
11–20	27	11	15	26	16	22
21–50	36	46	15	16	36	33
51–166	9	35	54	11	16	44
Mean percentage difference	19	35	61	11	21	37
Number of parallel titrations	11	26	13	19	31	18

* Percentage of the total parallel titrations in this group, which had percentage-differences of 0.16–10, etc.

For the parallel titrations in Table II, the Standard Deviation (S.D.) was 94.86 for trypsin, and the Standard Error (S.E.) 19.6. Therefore for differences in the results of trypsin titrations to be significant, they must be at least 58.8 units (3×S.E.). The Standard Deviation (S.D.) was 196 for amylase, and the Standard Error (S.E.) 36. Therefore for differences in the results of amylase titrations to be significant they must be at least 108 units (3×S.E.)

As may be seen in Table V the differences in trypsin and amylase activity during and after recovery from diarrhea were significant.

3. *The amount and dilution of enzyme* used are important factors in the reliability of the results. Usually a preliminary "trial and error" titration is necessary in order to avoid too fast or too slow a reaction. The results usually were more inaccurate if the time required for a 20 per cent reduction in the initial viscosity was less than 10 and more

TABLE IV

Examples of parallel amylase titrations of duodenal contents (fig. 2)

PATIENT (SPECIMEN) AND CURVE	AMOUNT (AND DILUTION) OF DUODENAL CONTENTS	TIME REQUIRED FOR 20% REDUCTION IN INITIAL VISCOSITY	AMYLASE UNITS PER CC. OF DUODENAL CONTENTS (60/t × dil.)	AVERAGE	DIFFERENCE	PERCENTAGE DIFFERENCE
	cc.	*min.*				
4 (V), curve 6 (fig. 2)	0.2 (1:7.5)	24.5	91.9	92.5	1.3	1.4
4 (V), curve 8 (fig. 2)	0.1 (1:7.5)	48.3	93.2			
8 (II), curve 7 (fig. 2)	0.1 (1:15)	27.7	325	328.5	7	2.1
8 (II), curve 9 (fig. 2)	0.1 (1:50)	90	332			

TABLE V

Evaluation by the standard error method of the trypsin and amylase values of duodenal contents during and after diarrhea (table I)

PATIENT, DATE, AND STATE OF DIGESTION (TABLE I)	AVERAGE NUMBER OF TRYPSIN UNITS	DIFFERENCE	THREE TIMES THE STANDARD ERROR FOR TRYPSIN (TABLE II)	AVERAGE NUMBER OF AMYLASE UNITS	DIFFERENCE	THREE TIMES THE STANDARD ERROR FOR AMYLASE (TABLE II)
1, 11/4, acute diarrhea	4.5	82	58.8	184.9	434	108
1, 12/3 and 12/4, complete recovery from diarrhea	86.6			618.9		

than 60 minutes. The amounts of duodenal contents used in these titrations varied from 0.05 to 0.2 cc., and the dilutions (made with normal saline) ranged from none for weak enzymes to 1:200 for potent ones.

4. *Variations of 1 or 2 degrees in the temperature* at which the enzymes are titrated change the rate of enzymic reactions. An accurately controlled water bath is necessary for comparable results.

5. *The substrates* greatly affect the results; a new lot of gelatin or of starch may be more or less rapidly hydrolyzed by the same amount of enzyme. The hydrogen-ion concentration (4, 10) and the concentration of the gelatin or starch also change the rate of enzymic reactions. All titrations should be made at the same reaction, with the same concentration of the same buffer, and with the same preparation and concentration of substrate. A starch suspension with a relative viscosity of approximately 2.5 and less than 12 hours old is the most suitable for the viscometric titration of amylase, but the results are not always accurate (7). Variability of the substrate also can be detected by testing it with an enzymic preparation of known activity.

6. *The end-products of the reaction* may interfere with the activity of the enzyme by combining with it or rendering it inactive (11).

7. *Accelerators and paralyzers:* Certain chemicals increase the activity of an enzyme, e.g. calcium chloride retards the inactivation of amylase and increases the rate of starch digestion (6, 12). Other substances inhibit enzymic activity by their effect on the enzyme or substrate or the reaction velocity, e.g. the salts of heavy metals (13).

8. *Light and radiation* influence enzymic reactions by destroying the enzyme itself or by modifying its activity (14).

9. *The calibers of the capillary tubes* of the Ostwald viscosimeters are never quite similar, and titrations made in different instruments may not be comparable. Only standard calibrated capillary tubing should be used. Fibers, hairs or dirt, which sometimes obstruct the tubes, are other important factors.

10. *The position of the collecting tube in the duodenum* is an important factor, and always should be determined by fluoroscopy. Specimens obtained just beyond the bend in the second portion of the duodenum may be four times as active as those collected just below the pylorus or in the terminal portion of the duodenum (15).

11. *The presence of gastric contents* greatly increases the enzymic activity of duodenal contents, not only by stimulating the pancreas, but also because gastric juice has an amylase-accelerating action (16). Gastric juice contamination may be reduced by Abbott's procedure of attaching a second balloon 1 or 2 inches above the duodenal bucket of a Miller-Abbott tube, and inflating it when the bucket is passed into the duodenum so that it becomes impacted in the pylorus (17). The usual

balloon of the Miller-Abbott tube, which is distal to the duodenal bucket, prevents the escape of duodenal contents into the jejunum.

12. *Changes in enzymic activity* occur if duodenal contents are kept one or more days, even when on ice with or without thymol. Usually the potency fell but occasionally it increased, probably through the action of the enzymes of infecting bacteria. In specimens kept for long periods, the amylase did not change in 3 months, but the tryptic activity decreased 50 per cent in 1 month. The time between the dilution of the enzyme and its assay also is a factor in accuracy, especially for trypsin (15). Titrations of fresh dilutions and of those allowed to stand for an hour or more usually are different.

In addition to the above difficulties which affect the enzymic titrations of duodenal contents, the amount of duodenal secretion and the enzymic activity of the specimens are subject to several variables. For example, if the patient is dehydrated, a much longer time is required to obtain the necessary 6 to 8 cc. of duodenal contents, and the enzymic assays sometimes are low (15). The patient's state of digestion has an important relation to the enzymic activity of duodenal contents, diarrhea and malnutrition being associated with a marked reduction in trypsin and amylase (1, 2, 3) (Table I). Diet, time after the last meal (fasting contents are more accurate) (15), age of the patient, hydrogen-ion concentration of the specimen, bacterial contamination, and fever have been discussed elsewhere (2, 18).

SUMMARY

Some of the difficulties in the titration of trypsin and amylase in duodenal contents are presented.

Thanks are due Dr. J. H. Northrop, Dr. D. H. Andersen and Dr. S. A. Waksman for helpful suggestions, Dr. Elizabeth Torrey (Mrs. J. G. Andrews) for plotting the enzymic curves and calculating the units, Miss Gertrude M. Cox, Mrs. J. W. Beard, and Dr. D. H. Sprunt for calculating the Standard Deviation and Standard Error, Mrs. H. A. King and Mr. E. H. Clark for the drawings, Mr. J. H. Neese and Mr. W. V. Singletary for verifying the calculations.

REFERENCES

1. ANDERSEN, D. H.: A Method for Assaying Trypsin which is Suitable for Routine Use in the Diagnosis of Congenital Pancreatic Deficiency (in press); idem: Pancreatic Enzymes in the Duodenal Juice in Celiac Syndrome, *Am. J. Dis. Child.*, 63: 643–658 (April) 1942.

2. DAVISON, W. C.: The Duodenal Contents of Infants in Health, and During and Following Diarrhea, *Am. J. Dis. Child.*, **29:** 743, 1925.
3. KAJDI, L., AND DAVISON, W. C.: Chemical and Enzymic Studies of the Duodenal Contents of Infants (in press).
4. NORTHROP, J. H., AND HUSSEY, R. G.: A Method for the Quantitative Determination of Trypsin and Pepsin, *J. Gen. Physiol.*, **5:** 353, 1923.
5. DAVISON, W. C.: A Viscometric Method for the Quantitative Determination of Amylase, *Bull. Johns Hopkins Hosp.*, **37:** 281, 1925; THOMPSON, W. R, JOHNSON, C. E., AND HUSSEY, R. G.: A Viscosimetric Method of Estimating Enzyme Concentration with Special Reference to Amylase, *J. Gen. Physiol.*, **15:** 1, 1931.
6. THOMPSON, W. R., TENNANT, R., AND WIES, C. H.: Studies in Starch Amylase Viscosimetry. I. A Sensitive Precision Method for the Estimation of Amylolytic Activity Applicable to Human Serum, *J. Biol. Chem.*, **108:** 85, 1935.
7. WIES, C. H., AND MCGARVEY, S. M.: A Study of the Effects of Certain Variations in the Preparation of a Starch Substrate in Amylase Viscosimetry, *J. Gen. Physiol.*, **16:** 221, 1932; THOMPSON, W. R., MCGARVEY, S. M., AND WIES, C. H.: A Reproducible Standard Substrate in Starch-Amylase Viscosimetry, *ibid.*: **16:** 229, 1932; DAVISON, W. C.: Relation of the Concentration of Starch Suspensions to their Viscosity (in press); idem: Relation of the Concentration of Starch Suspensions to their Use as Substrates for the Amylase of the Duodenal Contents of Infants (in press). Chesley, L. C.: The Validity of the Viscometric and Wohlgemuth Method for the Quantitative Determination of Amylase, *J. Biol. Chem.*, **92:** 171, 1931.
8. MASLOW, H. L., AND DAVISON, W. C.: A Comparison of the Viscometric, Copper Reduction, Polariscopic and Iodometric Methods for Measuring the Rate of Hydrolysis of Starch and Dextrin by Aspergillus oryzae, *J. Biol. Chem.*, **68:** 75, 1926.
9. ANSON, M. L.: Estimation of Pepsin, Trypsin, Papain, and Cathepsin with Hemoglobin, *J. Gen. Physiol.*, **22:** 79, 1938.
10. MASLOW, H. L. AND DAVISON, W. C.: The Effect of the Hydrogen-Ion Concentration upon the Starch-Liquefying Activity of the Amylase of Aspergillus oryzae, *J. Biol. Chem.* **68:** 83, 1926. Rothman, P. E., Widener, D. C., and Davison, W. C.: The Optimal Reaction for the Starch-Liquefying Activity of the Duodenal Amylase of Infants *Am. J. Dis. Child.* (in press).
11. NORTHROP, J. H.: The Effect of the Concentration of Enzyme on the Rate of Digestion of Proteins by Pepsin, *J. Gen. Physiol.* **2:** 471, 1920; also *Science*, **53:** 391, 1921.
12. NAKAMURA, H.: Amylase-protecting Substances: Takadiastase, Malt Amylase, Pancreas Amylase and Calcium, *J. Soc. Chem. Ind.*, Japan, **34:** 265, 1931.
13. WAKSMAN, S. A., AND DAVISON, W. C.: *Enzymes*, Williams and Wilkins Co., Baltimore, Md., 1926.

14. Hussey, R. G., and Thompson, W. R.: The Effect of Radioactive Radiations and X-rays on Enzymes, *J. Gen. Physiol.*, **6**: 1, 7, 1923; **9**: 211, 309, 315, 1925 and 1926; The Effect of Radiations from a Mercury Arc in Quartz on Enzymes, *J. Gen. Physiol.*, **9**: 217, 1925; **15**: 9, 1931.
15. Andersen, D. H.: Personal Communication.
16. Davison, W. C.: The Amylase-Accelerating Action of Gastric Contents, *Am. J. Dis. Child.*, **63**: 728, 1942.
17. Abbott, W. O.: Indications for the Use of the Miller-Abbott Tube, *New England J. M.*, **225**: 641, 1941.
18. Diamond, J. S., Siegel, S. A., and Kantor, J. L.: The Secretin Test in the Diagnosis of Pancreatic Diseases with a Report of One Hundred Thirty Tests, *Am. J. Digest. Dis.*, **7**: 435, 1940.

PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

HELD IN THE HURD MEMORIAL HALL, APRIL 13, 1942

The President of the Society, Dr. Frank B. Walsh, presided.

A symposium on the results of modern-day treatment of cancer was held, and the following papers were presented:

Ocular Melanoma. J. S. Friedenwald (Department of Ophthalmology)

Upper Respiratory Tract. E. N. Broyles (Department of Surgery)

Lip and Tongue. G. E. Ward (Department of Surgery)

Hopeless Breast Cancer. G. Farber (Department of Surgery)

Female Generative Tract. R. W. TeLinde (Department of Gynecology)

Prostate and Bladder. H. H. Young (Department of Urology)

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Skin Grafting. By EARL CALVIN PADGETT; 149 pp., illus. $4.50. *Charles C. Thomas, Springfield, Ill., 1942.*

This book is an excellent contribution on a phase of skin grafting. It is mainly a record of the author's experiences with a type of graft that can be cut consistently only by mechanical means such as the dermatome which he has devised. The author recognizes four varieties of free sheet grafts of skin. Two are well known to all surgeons, the Ollier-Thiersch graft and the graft of whole-thickness skin. However, as he points out, the Ollier-Thiersch graft, originally described as an epidermal graft, probably has never been cut. In practice it is a thin graft which contains more or less of the upper corium depending upon the inherent human factor and the impossibility of controlling absolutely the level of a hand-held knife, as well as upon the location from which the graft is being removed, and the nutrition, sex, age and even the race of the patient. It remained for Blair and Brown in 1929 to demonstrate the advantages of a deeper graft, the so-called split graft. This graft yields the high percentage of successful "takes" usually associated with the thinner grafts and at the same time a functional result comparable with the full-thickness graft. It is on the further use of the split or intermediate thickness graft that Padgett has written. His surgical contribution is a dermatome which facilitates the cutting of large (4 by 8 inches) sheets of skin of uniform thickness which can be varied by a calibrating mechanism. This apparatus permits the utilization of hitherto unavailable portions of the body as donor areas and the grafts themselves may be more exactly adapted to the surface needed.

Padgett writes with unquestioned authority on this type of graft. He describes completely its indications and contra-indications, the preparation of the recipient area and the after care.

This reviewer would prefer that this graft had not been described as a new graft. It is a graft of intermediate thickness as is the split graft of Blair and Brown, and has been used by many surgeons who have attempted more or less successfully to cut it free hand depending upon their own ability, the thickness of the donor site and the needs of the recipient area.

There are evidences of hurried proof-reading, and the illustration on page 27 of a method of cutting whole-thickness grafts would be improved if it were stated that the edge of the graft held by clamps should be discarded before the graft is applied. This book should be of great help to all surgeons who are called upon to graft skin. It is highly recommended.

E. M. H.

Modern Bread from the Viewpoint of Nutrition. By HENRY C. SHERMAN and CONSTANCE S. PEARSON. 118 pp. $1.75. *The Macmillan Company, New York, 1942.*

In this timely book, Dr. Sherman and Miss Pearson have discussed the subject of Modern Bread in a dispassionate fashion which is especially commendable at this time when many experts will not be dissuaded from their points of view that whole grain bread is the preferred staff of life, and exponents of the enrichment program are vociferous in their efforts to create a demand for enriched bread. The authors have set down all of the pertinent facts concerning bread. They have made clear the point that enriched bread is improved white bread and preferable to it. They have been intentionally vague in the summary as to their attitude toward white or enriched bread versus the whole grain product and have left it for the critical reader to draw his own conclusion.

The authors make clear the following facts. Actually, there are three grades of bread—white bread, enriched bread, and whole grain bread. Nutrition experts agree that while the new enriched bread is better in nutritional desirability than ordinary white bread, the most valuable bread is that in which the natural nutrients of the whole grain are retained.

E. R. T.

INDEX TO VOLUME LXX

Pagination According to Months:

January, 1942, pp. 1–100
February, 1942, pp. 101–200
March, 1942, pp. 201–333
April, 1942, pp. 335–397
May, 1942, pp. 399–465
June, 1942, pp. 467–522

Addison's disease, The electro-encephalogram in..... 335
p-Aminobenzoic acid as a metabolite essential for bacterial growth..... 19
Asthma, intractable bronchial, Further observations on the treatment of, by bilateral resection of the pulmonary plexus..... 386

Bard, Philip (see Woolsey, Clinton N.)..... 399
Basilar artery and its branches, Demonstration of the, with thorotrast..... 81
Berger, Olive L. (see Lyford, John, III)..... 488
Book Reviews..... 95, 193, 332, 396, 464, 518
Brown, J. Howard: A fungus culture slide..... 460
Brown, Thomas McP., and John C. Nunemaker: Rat-bite fever. A review of the American cases with reevaluation of etiology; report of cases..... 201
Broyles, Edwin N.: Anterior commissure tendon of the larynx. Its significance in the laryngofissure operation. Preliminary note..... 90
Buka, Robert (see Friedenwald, Jonas S.)..... 1

Cameron, Eugenia S. (see Tidwell, Herbert C.)..... 362
Carnes, William H.: The present incidence of tuberculous infection..... 101
Choline esterase content of the chorioid plexus and ciliary processes, The..... 14
Circulation, A study of mechanical factors in the, with special reference to the problem of acute circulatory failure..... 26

Davison, Wilburt C.: Difficulties in the enzyme titration of duodenal contents..... 504
Deaths, An analysis of, in the operating rooms of the Johns Hopkins Hospital with special reference to those occurring under general anesthesia and spinal anesthesia..... 488

Enzymes, The distribution of certain oxidative, in the chorioid plexus..... 1
Enzyme titration of duodenal contents, Difficulties in the..... 504

Fats, The relation between the chemical structure of, and their ability to produce gastric inhibition..... 362
Ford, Frank R. (see King, Arthur B.)..... 124
Friedenwald, Jonas S., Heinz Herrmann, and Robert Buka: The distribution of certain oxidative enzymes in the chorioid plexus..... 1
Friedenwald, Jonas S. (see Hermann, Heinz)..... 14
Fungus culture slide, A..... 460

Gay, Leslie N., and William F. Rienhoff: Further observations on the treatment of intractable bronchial asthma by bilateral resection of the pulmonary plexus.... 386
Gay, Leslie N. (see Iliff, Elizabeth H.).... 378
Gantt, W. Horsley, and Wendell Muncie: Analysis of the mental defect in chronic cases of Korsakov's psychosis by means of the conditioned reflex method.... 467
Gonococcus, The isolation and identification of the.... 370

Hay fever, Oral treatment of, with ragweed pollen.... 378
Herrmann, Heinz, and Jonas S. Friedenwald: The choline esterase content of the chorioid plexus and ciliary processes.... 14
Herrmann, Heinz (see Friedenwald, Jonas S.).... 14
Hoffman, W. Christie, Roger A. Lewis, and George W. Thorn: The electro-encephalogram in Addison's disease.... 335

Iliff, Elizabeth H., and Leslie N. Gay: Oral treatment of hay fever with ragweed pollen.... 378

Johns Hopkins Medical Society, Proceedings of the meeting of the 92, 187, 329, 394, 463, 517

King, Arthur B.: Demonstration of the basilar artery and its branches with thorotrast.... 81
King, Arthur B., and Frank R. Ford: A clinical and anatomical study of neurological conditions resulting from metastases in the central nervous system due to carcinoma of the lung.... 124
Kolb, Lawrence (see Sullivan, Maurice).... 177
Korsakov's psychosis, Analysis of the mental defect in chronic cases of, by means of the conditioned reflex method.... 467

LaRochelle, Frederick T. (see Price, Philip B.).... 26
Larynx, anterior commissure tendon of the. Its significance in the laryngofissure operation. Preliminary note.... 90
Lewis, Roger A. (see Hoffman, W. Christie).... 335
Lipoids, from beef brains, The reaction of the subcutaneous tissues to the acetone insoluble.... 55
Lung, carcinoma of the, A clinical and anatomical study of neurological conditions resulting from metastases in the central nervous system due to.... 124
Lyford, John, III, Olive L. Berger, and Harris B. Shumacker, Jr.: An analysis of deaths in the operating rooms of the Johns Hopkins Hospital with special reference to those occurring under general anesthesia and spinal anesthesia.... 488

Marshall, Wade H. (see Woolsey, Clinton N.).... 399
Muncie, Wendell (see Gantt, W. Horsley).... 467

Nicholls, Jane (see Sullivan, Maurice).... 177
Nunemaker, John C. (see Brown, Thomas McP.).... 201
Nutritional dermatoses in the rat. VII. Notes on the posture, gait and hypertonicity resulting from a diet containing unheated, dried egg white as the source of protein.... 177

Park, Charles R., and W. Barry Wood, Jr.: *p*-Aminobenzoic acid as a metabolite essential for bacterial growth 19
Price, Philip B., Herbert E. Sloan, Jr., and Frederick T. LaRochelle: A study of mechanical factors in the circulation, with special reference to the problem of acute circulatory failure 26

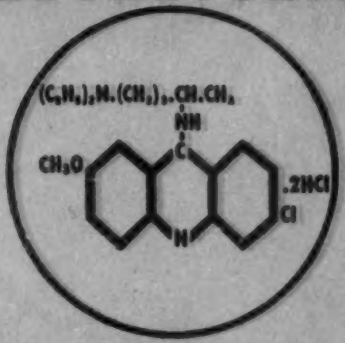
Rat-bite fever. A review of the American cases with reevaluation of etiology 201
Reid, Roger D.: The isolation and identification of the gonococcus 370
Richter, Curt P., and Bettye G. Woodruff: Facial patterns of electrical skin resistance; their relation to sleep, external temperature, hair distribution, sensory dermatomes and skin disease 442
Rienhoff, William F. (see Gay, Leslie N.) 386

Serum albumin, Dietary protein and the regeneration of. IV. The potency values of dried beef serum, whole egg, cow's milk, cow's colostrum, lactalbumin, and wheat gluten 157
Shumacker, Harris B. (see Lyford, John, III) 488
Skin resistance, facial patterns of electrical; their relation to sleep, external temperature, hair distribution, sensory dermatomes and skin disease 442
Sloan, Herbert E., Jr. (see Price, Philip B.) 26
Sullivan, Maurice, Lawrence Kolb, and Jane Nicholls: Nutritional dermatoses in the rat. VII. Notes on the posture, gait and hypertonicity resulting from a diet containing unheated, dried egg white as the source of protein 177

Tactile sensibility, cutaneous, Representation of, in the cerebral cortex of the monkey as indicated by evoked potentials 399
Thorn, George W. (see Hoffman, W. Christie) 335
Tidwell, Herbert C., and Eugenia S. Cameron: The relation between the chemical structure of fats and their ability to produce gastric inhibition 362
Tompkins, Edna H.: The reaction of the subcutaneous tissues to the acetone insoluble lipoids from beef brains 55
Tuberculous infection, The present incidence of 101

Weech, A. A.: Dietary protein and the regeneration of serum albumin. IV. The potency values of dried beef serum, whole egg, cow's milk, cow's colostrum, lactalbumin, and wheat gluten 157
Wood, W. Barry, Jr. (see Park, Charles R.) 19
Woodruff, Bettye G. (see Richter, Curt P.) 442
Woolsey, Clinton N., Wade H. Marshall, and Philip Bard: Representation of cutaneous tactile sensibility in the cerebral cortex of the monkey as indicated by evoked potentials 399

Synthesis IN OUR LABORATORIES



Acute attacks of malaria are checked rapidly — within a day or two.... Parasites in the blood stream disappear quickly — in a week or less.... The dose is small — in the average adult case only 1½ grains three times daily for five days.

Antimalarial Specific

ATABRINE

BRAND OF QUINACRINE

DIHYDROCHLORIDE

WINTHROP CHEMICAL COMPANY, INC.

NEW YORK, N. Y. WINDSOR, ONT.

Are the Neuritic Symptoms of Pregnancy *due to a deficiency of vitamin B_1 (thiamine)?*

SUCH common neuritic symptoms of pregnancy as pains in arms and legs, muscle weakness, and (less frequent but more serious) paralysis of the extremities may result from a shortage of antineuritic vitamins, recent investigations appear to show. Although neuronitis of pregnancy has long been considered a toxemia, no toxins have ever been identified.

Clinical observations of Strauss and McDonald lead to the conclusion that the condition is a dietary deficiency disorder similar to beriberi, caused by lack of vitamin B_1. They report recovery in their cases receiving this therapy, including dried brewers' yeast.

Hyperemesis as Cause of Avitaminosis

Wechsler observes that all cases of polyneuritis of pregnancy recorded in the literature were preceded by long periods of severe vomiting. "It would seem," he adds, "that because of actual starvation these patients suffered from avitaminosis and consequent neuritis," a view likewise held by Hirst, Luikart, and Gustafson. Plass and Mengert observe that the practice of giving high carbohydrate feedings for hyperemesis gravidarum is still more likely to cause avitaminosis.

Dried brewers' yeast, as it is far richer than any other food in vitamin B_1 (thiamine), is being used with benefit both in the prevention and treatment of polyneuritic symptoms of pregnancy. Lewy found that additions of yeast to the diet reduced electric irritability of the peripheral nerves and brought clinical improvement. Vorhaus states that he and his associates, after administering large amounts of vitamin B_1 (thiamine) to 250 patients having various types of neuritis, including that of pregnancy, observed in about 90% of cases "varying degrees of improvement, i.e., from partial relief of pain to complete disappearance of all symptoms."

Need for Vitamin B_1 (thiamine) in Lactation

Evans and Burr, Hartwell, Sure and co-workers, and Macy *et al* are among numerous authorities who find that the nursing mother also needs a supplement of vitamin B_1 (thiamine) from 3 to 5 times the normal requirement. It is accepted that during pregnancy and lactation the requirement for vitamin G (riboflavin) is increased.

Consisting of nonviable yeast, Mead's Brewers Yeast Tablets offer not less than 50 International vitamin B_1 (thiamine) units and 50 Sherman vitamin G (riboflavin) units per gram (20 International units of vitamin B_1 and 20 Sherman units of vitamin G per tablet).

Supplied in bottles of 250 and 1,000 tablets, also in 6-oz. bottles of powder.

Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.

Mead Johnson & Company, Evansville, Indiana, U. S. A.